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Cellular pathogenesis of Duchenne muscular dystrophy: progressive myofibre degeneration, chronic inflammation, reactive myofibrosis and satellite cell dysfunction

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Abstract

Duchenne muscular dystrophy is a highly progressive muscle wasting disease of early childhood and characterized by complex pathophysiological and histopathological changes in the voluntary contractile system, including myonecrosis, chronic inflammation, fat substitution and reactive myofibrosis. The continued loss of functional myofibres and replacement with non-contractile cells, as well as extensive tissue scarring and decline in tissue elasticity, leads to severe skeletal muscle weakness. In addition, dystrophic muscles exhibit a greatly diminished regenerative capacity to counteract the ongoing process of fibre degeneration. In normal muscle tissues, an abundant stem cell pool consisting of satellite cells that are localized between the sarcolemma and basal lamina, provides a rich source for the production of activated myogenic progenitor cells that are involved in efficient myofibre repair and tissue regeneration. Interestingly, the self-renewal of satellite cells for maintaining an essential pool of stem cells in matured skeletal muscles is increased in dystrophin-deficient fibres. However, satellite cell hyperplasia does not result in efficient recovery of dystrophic muscles due to impaired asymmetric cell divisions. The lack of expression of the full-length dystrophin isoform Dp427-M, which is due to primary defects in the DMD gene, appears to affect key regulators of satellite cell polarity causing a reduced differentiation of myogenic progenitors, which are essential for myofibre regeneration. This review outlines the complexity of dystrophinopathy and describes the importance of the pathophysiological role of satellite cell dysfunction. A brief discussion of the bioanalytical usefulness of single cell proteomics for future studies of satellite cell biology is provided.

Key Words: dystrophinopathy, fibrosis, immune response, myoblast, stem cell.

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This review on the cellular pathogenesis of Duchenne muscular dystrophy (DMD) is part of the Special Issue on 'Muscle Satellite Cells in Health and Disease' in the European Journal of Translational Myology, edited by Massimo Ganassi and Zipora Yablonka-Reuveni.[1] The quintessential satellite cell (SC) population, discovered independently in 1961 by Alexander Mauro and Bernard Katz,[2-5] represents resident myogenic stem cells in skeletal muscles.[6-8] SCs are of central importance for supporting neuromuscular homeostasis, myofiber maintenance, muscle plasticity and the high degree of adaptability of the voluntary contractile system to changed functional demands, as well as the remarkable regenerative capacity of skeletal muscles that underlie the self-repair capabilities of myofibres following traumatic injury, chronic disease or aging-related functional decline.[9-11] Interestingly, during myofiber regeneration in long-term denervated muscles, the relative number of SCs remains at a high level.[12,13] Morphological studies have shown that the regeneration of contractile fibres plays a crucial role in the maintenance of chronically denervated skeletal muscles. Replication of SCs clearly occurs after drug-induced muscle damage, using repeated applications of the local anaesthetic and nerve blocking agent bupivacaine, even in the absence of reinnervation.[12]

The self-renewal of SCs is finely regulated in order to maintain an essential stem cell pool in matured skeletal muscles.[7] This process is balanced with the production of myogenic progenitor cells,[8] which are involved in

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efficient myofibre repair and regeneration.[14] A disturbance of this delicate balance between symmetric versus asymmetric cell division of activated SCs causes a diminished regenerative capacity and thus plays a crucial role in neuromuscular pathology.[10] This article focuses on the pathophysiological complexity of DMD and provides an overview of the role of SC dysfunction as a critical part of the overall damage pathway that leads to contractile weakness in dystrophic muscles.[15] Abnormal functioning of the resident stem cell pool in dystrophin-deficient muscle fibres appears to be of central importance for the weakened regenerative capacity of dystrophic myofibres,[16-19] making it an integral part of the major symptoms of dystrophinopathy, i.e. progressive skeletal muscle degeneration, fat replacement, reactive myofibrosis and chronic sterile inflammation.[20-22]

In this review, we outline the pathophysiological mechanisms that involve fibre necrosis, myofibrosis, a sustained immune response and SC dysfunction, and briefly outline the relevance of these destructive processes for the development and innovative design of novel therapies to treat dystrophin deficiency. For the selection of up-to-date publications to be discussed in this article on dystrophinopathy, the roles of myonecrosis, myofibrosis, inflammation and SC dysfunction were reviewed by literature screening using a combination of search terms, such as 'dystrophin', 'necrosis', 'myonecrosis' 'fibrosis', 'myonecrosis', 'inflammation' 'satellite cell', 'myoblast', 'dystrophinopathy' and 'Duchenne muscular dystrophy' in the Pubmed database. The identified list of publications was then further screened for their relevance to this review of the molecular and cellular pathogenesis of DMD.

Dystrophinopathy

DMD is an X-chromosomally inherited and highly progressive muscular disorder of early childhood.[23] Primary defects in the *DMD* gene trigger the almost complete loss of the membrane cytoskeletal protein named dystrophin.[24] However, a large number of promoters produce a variety of tissue-specific dystrophin protein isoforms.[25] Thus, depending on individual mutations within the extremely large *DMD* gene, in combination with genetic modifiers, the bodily functions of Duchenne patients can be affected in a variety of ways.[26-28] Besides skeletal muscle wasting, multi-systemic complications can occur, including late-onset cardio-respiratory syndrome,[29] neuronal abnormalities,[30] and dysfunction of the kidneys, bladder, liver, digestive tract and the immune system.[31] Here, we focus on the complexity of progressive skeletal muscle degeneration.

Figure 1 outlines the promoter structure of the human *DMD* gene, the major domains of the full-length Dp427-M protein isoform of dystrophin that is expressed in myofibres, and the localization of the various components of the dystrophin-associated glycoprotein complex at the sarcolemma. The core dystrophin complex consists of α/β-dystroglycan, α/β/γ/δ-sarcoglycan, sarcospan, α/β-syntrophin and α-dystrobrevin.[32] The tight linkage between the α/β-dystroglycan sub-complex and Dp427-M bridges the plasmalemma membrane and provides a stabilizing protein assembly between the sub-sarcolemmal actin cytoskeleton and the laminin-211 complex, which in turn binds collagen isoform COL-IV of the basal lamina.[33] Importantly, this indirect association between the intracellular cytoskeleton and the extracellular matrix prevents excess damage to the fibre periphery during repeated excitation-contraction-relaxation cycles or rigorous muscle stretching in normal muscle.[32,34]

As listed in Figure 1, the major functions of the core dystrophin complex include the provision of a trans-sarcolemmal linkage, the stabilization of the myofibre periphery, the organization of the intracellular network of cytoskeletal elements, the facilitation of a sarcolemmal signalling hub and the mechanical support for lateral force transmission at costamere structures.[34] Hence, a better understanding of the loss of dystrophin-associated proteins due to dystrophin deficiency and their involvement in the molecular and cellular pathogenesis of dystrophinopathy is critical for the identification of novel therapeutic targets and the development of new strategies to treat X-linked muscular dystrophy, such as improved pharmacological interventions, stem cell therapy and/or gene therapy.[35-38] Furthermore, biomarker discovery is of central importance for the improved diagnosis, prognosis and therapeutic monitoring of DMD.[39-41]

Chronic myofibre degeneration

Myonecrosis is the pathophysiological initiator of the complex degenerative processes that occur in dystrophic muscle fibres.[22,23] The absence of dystrophin partially eliminates the molecular anchoring capacity of the sarcolemma and thereby causes the loss of the dystrophin-associated glycoprotein complex.[42-44] The reduced expression of dystroglycans, sarcoglycans, dystrobrevins, syntrophins and sarcospan triggers impaired sarcolemmal integrity due to the loss of the linkage between laminin-211 and cortical γ-actin.[33] Weakened costameres result in diminished lateral force transmission and lessened load bearing capacity. Contraction-induced micro-rupturing of the surface membrane system damages the cellular unity of the muscular system. Sarcolemmal disintegration,[45] was shown to be directly linked to a calcium-dependent damage pathway in X-linked muscular dystrophy.[46] Ca^{2+}-ions flux through the disrupted plasmalemma and Ca^{2+}-leak channels, which causes chronically elevated Ca^{2+}-levels in the sarcosol. In conjunction with impaired luminal Ca^{2+}-buffering,[47,48] this triggers Ca^{2+}-dependent proteolysis leading to myofiber degradation,[49] as summarized in Figure 2.

The systematic analysis of dystrophic animal models, such as dystrophin-lacking mice, dogs or pigs,[50-52] was

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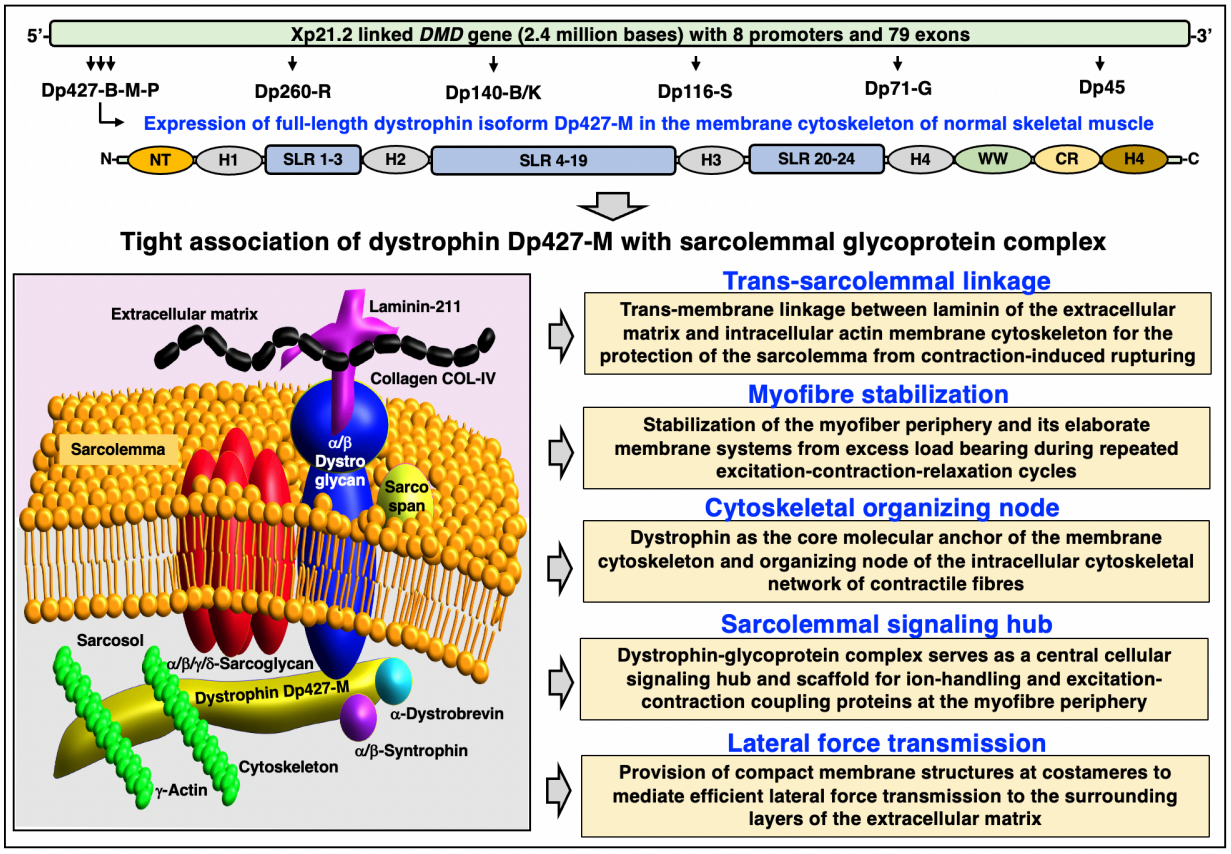

Fig 1. *The DMD gene and its protein product dystrophin- The diagram gives an overview of (i) the DMD gene that is defective in Duchenne muscular dystrophy, (ii) the major domains of the dystrophin protein product of this extremely large X-chromosomal gene and (iii) the structure of the dystrophin-associated glycoprotein complex in skeletal muscles. Eight promoters are involved in the tissue-specific expression of dystrophins, i.e. isoforms Dp427-M (muscle), Dp427-P (Purkinje cells), Dp427-B (brain), Dp260-R (retina), Dp140-B/K (brain/kidney), Dp116-S (Schwann cells), Dp71-G (ubiquitous) and Dp45 (brain). The full-length dystrophin protein isoform Dp427-M, which functions as a membrane cytoskeletal protein in the subsarcolemmal region, consist of a distinct amino-terminal domain (NT) with a major actin-binding site, four proline-rich hinge regions named H1-H4, three spectrin-like rod domains named SLR1-3, SLR4-19 and SLR20-24, a conserved WW region with tryptophan residues, a cysteine-rich CR domain and a carboxy-terminus (CT). Dystrophin forms a tight sarcolemma-associated complex with α/β-dystroglycans, α/β/γ/δ-sarcoglycans, sarcospan, α-dystrobrevin and α/β-syntrophins. The dystrophin/dystroglycan-provided linkage between laminin-211 and cortical γ-actin mediates an indirect connection between the collagen-containing extracellular matrix and the intracellular cytoskeleton. Besides being involved in the continued stabilization of the myofibre periphery during excitation-contraction-relaxation cycles, additional functions of the dystrophin-glycoprotein complex include the provision of an organizing hub for the membrane cytoskeleton and its connections to the intracellular cytoskeleton, the facilitation of a sarcolemmal signalling hub and mechanical support for lateral force transmission at costameres.*

crucial for the elucidation of myonecrosis and associated degenerative processes in muscular dystrophy.[53,54] Various *mdx*-type mouse models are frequently used for biomarker discovery, the identification of novel therapeutic targets and the testing of experimental treatments.[55-57] Proteome-wide alterations in dystrophin-deficient muscle specimens were shown to include characteristic abundance changes in proteins involved in excitation-contraction coupling, the contraction-relaxation cycle, ion homeostasis, bioenergetic pathways, the cellular stress response, the cytoskeleton, signalling cascades, membrane repair, and the extracellular matrix.[49,57]

The diagram in Figure 2 gives an overview of the complexity of dystrophinopathy, including the pathophysiological role of tissue scarring, loss of muscle elasticity, substitution with non-contractile cells, impairment of the regenerative capacity of dystrophic

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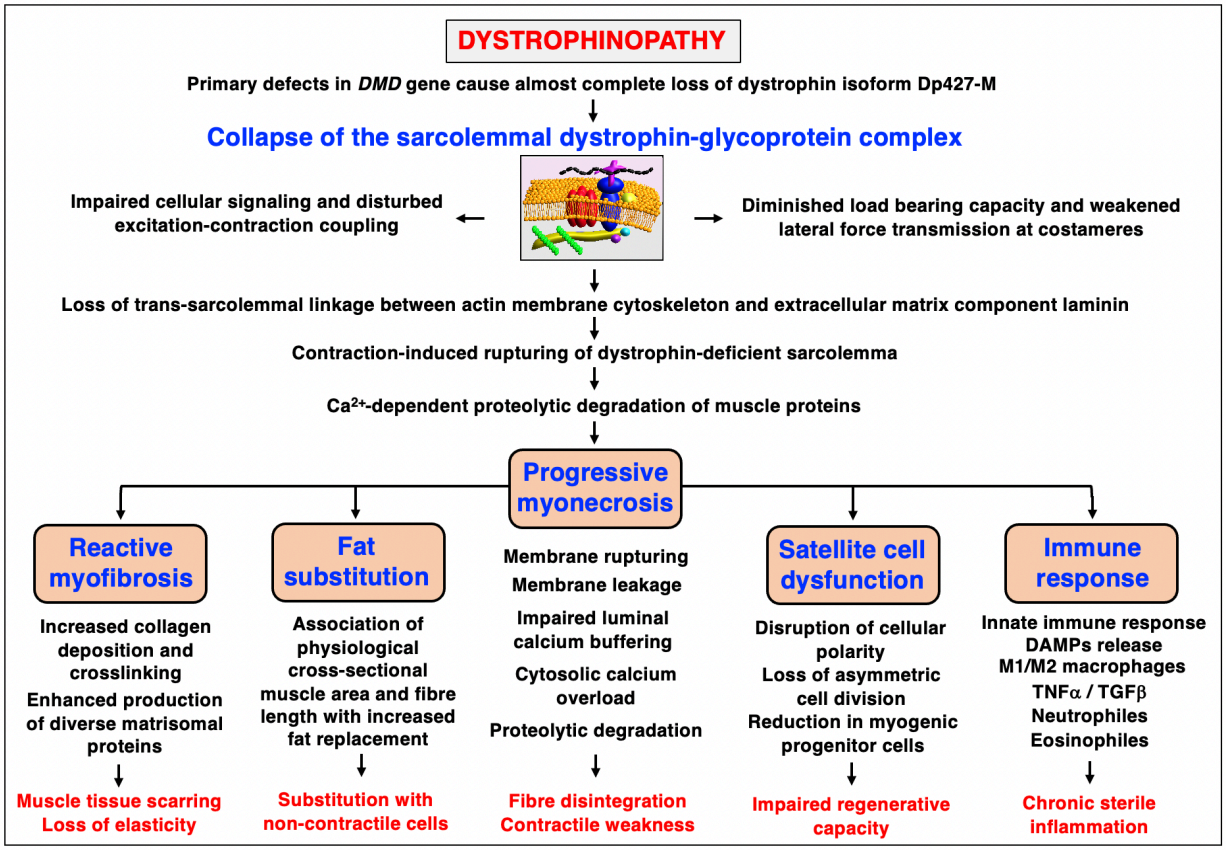

Fig 2. *Overview of the highly complex pathogenesis of muscle wasting in Duchenne muscular dystrophy The flowchart summarizes the complex pathophysiological changes in dystrophin-deficient skeletal muscle. The almost complete loss of the dystrophin isoform Dp427-M causes the loss of sarcolemmal integrity and contraction-induced membrane rupturing, which in turn results in abnormal sarcosolic calcium handling and associated proteolytic degradation of muscle proteins. Progressive myonecrosis is associated with a sustained immune response, fat replacement and reactive myofibrosis, as well as satellite cell dysfunction. This triggers myofiber disintegration, chronic inflammation, substitution with non-contractile cells, tissue scarring and an impaired regenerative capacity in dystrophic skeletal muscles.*

muscles and chronic sterile inflammation.[58] These changes in muscle integrity are related to exacerbated immune responses, fibre necrosis, fat replacement, reactive myofibrosis and SC dysfunction,[59] as described in below sections.

Chronic sterile inflammation

In DMD, a sustained immune response can be observed as a reaction to progressive fibre necrosis,[20] involving initially mostly the innate immune system.[60] However, crosstalk signalling exists between the innate immune response and T-cell adaptive immunity within the skeletal muscular system.[61,62] Within the lymphatic system, striking morphological changes were shown to occur in lymph nodes in association with muscular dystrophy. This affects especially the white pulp region of the spleen. In the dystrophic organism, the abundance of splenic inflammatory monocytes changes and immune cells migrate at an elevated rate from their splenic reservoir to dystrophin-deficient myofibres.[63] The systematic and mass spectrometry-based proteomic screening of spleen specimens from the *mdx-4cv* mouse model of dystrophinopathy confirmed this crosstalk between lymphoid organs and dystrophic skeletal muscles.[64,65] Splenic monocyte transfer to damaged myofibres and their subsequent differentiation into macrophages is a crucial underlying factor for chronic inflammation in muscular dystrophy.[66] Prolonged M1 and M2 macrophage activity,[67] based on both resident macrophages and infiltrating myocytes, and cytokine release are associated with a chronic inflammatory state of dystrophic fibres.[68] The massive infiltration of dystrophic fibres by macrophages, neutrophiles and dendritic cell populations is mediated by extensive cytokine and chemokine signalling events.[59,62]

The transforming growth factor TGF-β is released from M2 macrophages and initiates the activation of stromal cells that can adapt to multiple cellular lineages,[69]

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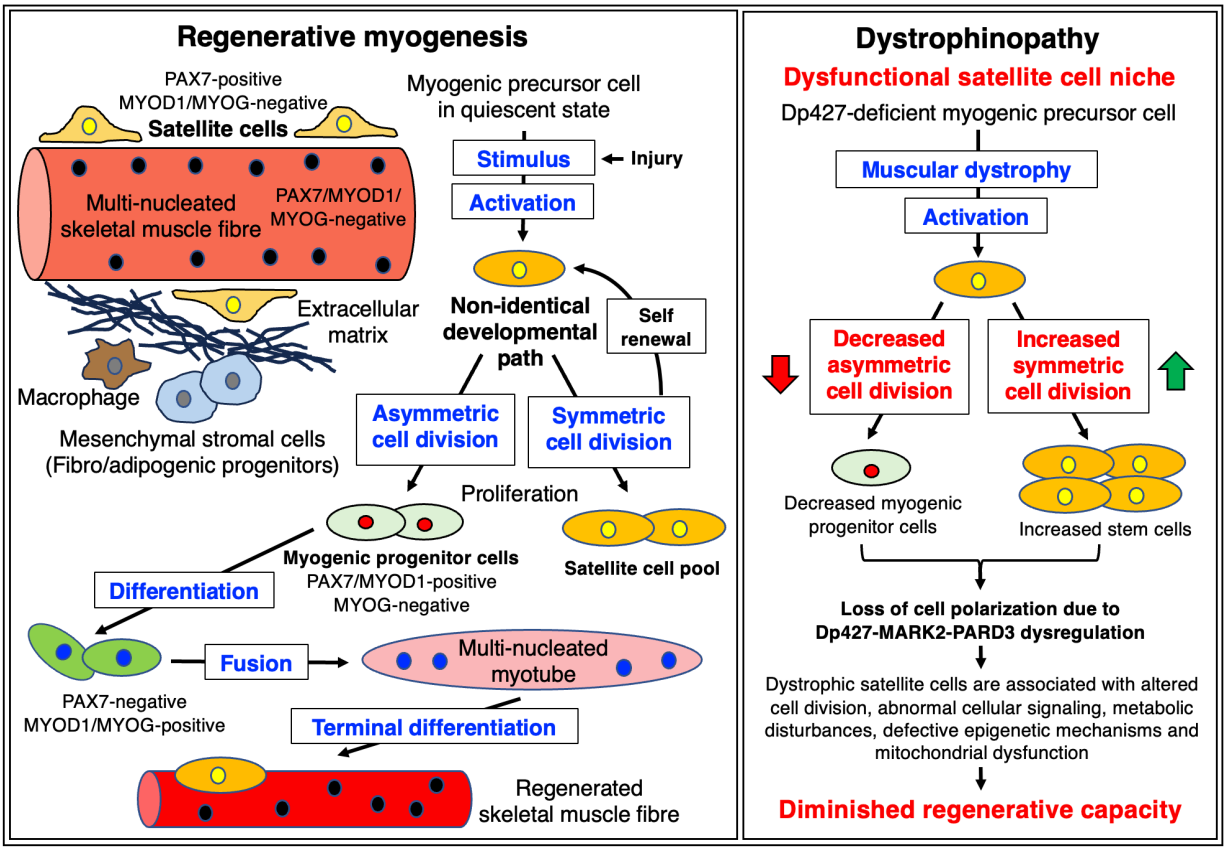

Fig 3. *Satellite cell dysfunction in Duchenne muscular dystrophy., The left panel of the diagram gives an overview of the main cell types and developmental steps involved in regenerative myogenesis in normal adult skeletal muscles following an appropriate stimulus, such as injury to the multi-nucleated skeletal muscle fibre system. Hierarchical alterations in transcription factor expression patterns, including PAX7 (paired box 7), MYOD1 (myoblast determination protein 1) and MYOG (muscle-specific transcription factor myogenin), can be observed during cellular changes. The dormant muscle stem cell population consisting of non-activated satellite cells, which are located between the sarcolemma and basal lamina, is PAX7-positive and MYOD1/MYOG-negative. Cellular proliferation is based on a non-identical developmental path that replenishes the satellite cell pool via symmetric cell division and produces via asymmetric cell division myogenic progenitor cells, which are PAX7/MYOD1-positive and MYOG-negative. Cellular differentiation results in PAX7-negative and MYOD1/MYOG-positive myoblasts that fuse to form multi-nucleated myotubes for efficient muscle repair. In contrast, the right panel of the diagram provides a pathophysiological scheme that outlines the potential mechanisms that underlie satellite cell dysfunction in dystrophinopathy. A variety of studies have shown that dystrophin-deficient stem cells undergo on the one hand increased symmetric cell division that causes a certain degree of satellite cell hyperplasia, and on the other hand are characterized by decreased asymmetric cell division which results in drastically lower levels of myogenic progenitor cells. The loss of stem cell polarization appears to be related to abnormal interactions between the greatly reduced levels of dystrophin Dp427-M, the microtubule affinity regulating serine-threonine kinase MARK2 and the partitioning defective protein PARD3 (partitioning defective protein 3). This type of satellite cell dysregulation is postulated to play a key role in the diminished regenerative capacity of skeletal muscles in Duchenne patients.*

including the important class of fibro-adipogenic progenitors (FAPs).[70-72] The FAPs type of cells participates in the generation of fibroblasts, myofibroblasts and adipocytes following activation by myofibre disintegration.[73] Prolonged periods of myofibre damage are associated with the shedding of characteristic components of damage-associated molecular patterns (DAMPs) including ATP and nucleic acids.[74] The innate immune system recognizes DAMP molecules and triggers an inflammatory response involving nuclear factor NF-κB and the inflammasome.[20] Peptides or protein fragments frequently leak through the damaged

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and dystrophin-deficient sarcolemma. These muscle-derived molecules may act as neo-antigens in the body and can be recognized by the adaptive immune system, causing additional immunological reactions.[60]

Reactive myofibrosis and fat replacement

Chronic inflammation and reactive fibrosis appear to be closely linked in damaged myofibres, whereby the innate immune response was shown to be involved in the recruitment of large numbers of myofibroblasts.[75] Myofibroblasts are of central importance for fibrotic changes due to their enhanced synthetic capacity for the production of matrisomal proteins in muscular dystrophy.[76] Elevated levels of extracellular matrix protein secretion trigger endomysial fibrosis,[77] which is characterized by classical histopathological features of dystrophic muscles, including fibro-fatty scars that surround myofibres and thereby inhibit proper mechano-transduction processes.[58,78]

Skeletal muscle scarring and a general loss of tissue elasticity due to reactive myofibrosis are characteristic signs of dystrophinopathy.[21] The aged *mdx-4cv* mouse diaphragm muscle has been extensively surveyed as a highly suitable surrogate for studying reactive myofibrosis in X-linked muscular dystrophy using extracellular matrix proteomics.[79] As listed in Figure 2, major pathobiochemical features of myofibrosis include a drastic increase in collagen deposition and crosslinking, as well as the enhanced production of diverse matrisomal proteins. Elevated levels were established for the matricellular protein periostin, the repair proteins annexin-2 and annexin-6, nidogen, fibronectin, dermatopontin, vitronectin, the small leucine-rich proteoglycans asporin, biglycan, decorin, lumican and mimecan, as well as various collagens, including COL-IV, COL-VI, COL-XV and COL-XVIII.[21,57,80] This makes fibrosis an important therapeutic target in muscular dystrophy,[81] as outlined in below section on treatment strategies to counteract dystrophic symptoms. Of note, adipogenic precursors appear to participate in interstitial remodelling in muscular dystrophy resulting in aberrant adipogenesis. This process might play a role in linking myofibrosis to fat substitution in dystrophic muscles.[82] Increased fat replacement is associated with alterations in physiological cross-sectional muscle area and myofibre length,[83,84] resulting in abnormal contractile functions and metabolic disturbances.[85]

Satellite cell dysfunction

As summarized in Figure 2, stem cell dysfunction plays a crucial part in the dystrophic pathogenesis and involves the disruption of cellular polarity, the loss of asymmetric cell division and a reduction in properly activated myogenic progenitor cells.[15,86] In contrast to multi-nucleated and large sized myofibres, muscle stem cells (MuSCs) are a small, mono-nucleated and multi-potent cell type that is positioned between the sarcolemma and basal lamina of mature skeletal muscle fibres.[6-8] The pool of available MuSCs is provided by a highly regulated process of self-renewal,[7] and combined with the essential creation of myogenic progenitor cells,[8] for repair and regeneration of adult myofibres.[14]

Figure 3 outlines the main steps involved in regenerative myogenesis. The presence of major myogenic factors, such as PAX7 (paired box 7),[87] MYOD1 (myoblast determination protein 1),[88] and MYOG (muscle-specific transcription factor myogenin),[89] are reliable markers of the various cell types,[90] that are involved in the regeneration of adult myofibres.[91] MYOG signalling is intrinsically involved in SC homeostasis and myocyte fusion.[92] While adult multi-nucleated skeletal muscle fibres are negative for PAX7, MYOD1 and MYOG, mono-nucleated myogenic precursor cells in their quiescent state are PAX7-positive. Myogenic progenitor cells produced by asymmetric division are PAX7/MYOD1-positive, but MYOG-negative. Following differentiation, these cells become PAX7-negative and MYOD1/MYOG-positive. The integration of signals that originate from the muscle environment trigger distinct changes in gene expression patterns based on complex epigenetic mechanisms, including nucleosome repositioning and post-translational modifications of chromatin.[93] Cellular fusion produces multi-nucleated myotubes, which then form regenerated myofibres by terminal differentiation.

The various cellular conversions can be conveniently followed by hierarchical alterations in transcription factor expression, including the general and not muscle-specific transcription factor FOXO (forkhead box O). Stem cell activation includes the following protein expression changes from quiescent SCs (positive for PAX7 and FOXO; but negative for MYF5, MYOD1 and MYOG) to activated SCs (positive for PAX7, MYF5 and MYOD1; but negative for FOXO and MYOG) to myoblasts (positive for PAX7, MYF5 and MYOD1; but negative for FOXO and MYOG) to myocytes (positive for MYOD1 and MYOG; but negative for PAX7, FOXO and MYF5). Therefore, patho-physiological scenarios with abnormal functioning of MuSCs in neuromuscular disease,[1] and/or diminished rates of stem cell differentiation are critical.[94] This can involve skeletal muscle precursor cells and their biological roles in a large variety of cellular processes, such as self-repair of damaged skeletal muscle fibres in association with muscle diseases, traumatic injury and neuromuscular aging,[9-11] as well as the maintenance of cellular homeostasis, muscle adaptations to changed contraction patterns and myofibre regeneration.[95-98]

Since stem cell dysfunction and regenerative exhaustion was shown to play a central role in X-linked muscular dystrophy,[99] mayor studies with a focus on SC abnormalities in dystrophin-deficient muscles are listed in Table 1.[16-19,57,100-122] Some of the contradictory findings on changes in SC numbers in dystrophic muscles from Duchenne patients and animal models of dystrophinopathy may be due to methodological

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Table 1. *List of major studies focusing on satellite cell and myogenic precursor cell dysfunction in dystrophinopathy.*

Bioanalytical approach	Skeletal muscle specimens	Characterization of skeletal muscle cells	References
Quantitative cell biological and ultrastructural analysis of SCs from dystrophic patients	Various muscle samples from patients ranging from preclinical to advanced stages of Duchenne muscular dystrophy	Increased number of SCs in dystrophin-deficient myofibre populations; type I fibres exhibit higher numbers of PAX7-positive SCs as compared to type II fibres	Wakayama et al.,[100]; Ishimoto et al.,[101]; Watkins and Cullen,[102,103]; Kottlors and Kirschner,[104]; Bankolé et al.,[105]
Replicative life-span analysis of SCs from dystrophic patients	Isolated SCs of muscle specimens from 2-7 year old Duchenne patients	Age-related decline in replicative capacity of isolated and dystrophin-deficient SCs	Webster and Blau,[106]
Evaluation of regenerative capacity in dystrophic muscles	Primary cultures, isolated myofibres, 3-month old *extensor digitorum longus* and 6-month old diaphragm of *mdx-23* mouse	Demonstration of latent regenerative capacity in dystrophic muscles	Yablonka-Reuveni and Anderson,[16]; Boldrin et al.,[107]; Matecki et al.,[108]
Histological, biochemical and molecular biological analysis of SCs in dystrophic muscles	*Gastrocnemius* from 3-month old *mdx-23* mouse, as compared to *DMD^{mdx}/ Large^{myd}* double mutant	Retention of PAX7-positive SC pool and proliferative capacity, but incomplete myofiber maturation and lack of preventing muscle degeneration	Ribeiro et al.,[18]
Analysis of Notch signaling in SCs	Myofiber preparations from *extensor digitorum longus* of 2-month old *mdx-23* mice	Increased SCs in young *mdx-23* mice, followed by age-related decrease in SCs and Notch signalling deficiency	Jiang et al.,[109]
Comparative analysis of SCs in *mdx-23* versus *mdx*/utrophin-/- dKO mice	*Extensor digitorum longus* from 2-month old mouse models	Depletion of SCs in severely dystrophic dKO mice, as compared to milder *mdx-23* phenotype	Lu et al.,[110]
Cell biological analysis of dystrophin in SCs	*Tibialis anterior, soleus* and *extensor digitorum longus* from mature Wistar rats	Presence of dystrophin isoform Dp427-M in normal SCs	Zhang and McLennan,[111]
Analysis of epigenetic activation of SCs commitment in dystrophin-deficient muscles	*Tibialis* anterior and *extensor digitorum longus* from 2-month old *mdx-23* mice	Asymmetric division of SCs involves MYF5 activation by PAX7, depending on CARM1, a specific substrate of p38γ/MAPK12. Dysregulation of p38γ/CARM1 signaling occurs in *mdx-23* muscles	Chang et al.,[112]
Cell biological analysis of dystrophin in dystrophic muscles	*Tibialis anterior* from 3-month old *mdx-23* mouse	Demonstration of association of dystrophin deficiency with decrease in the cell polarity regulators MARK2 and PARD3	Dumont et al.,[17]
Transcriptomic analysis of *mdx* myoblasts	*Gastrocnemius*-derived myoblasts from 2-month old *mdx-23* and *mdx-βgeo* mice, and Duchenne patient myoblasts	Significant alteration of gene expression including *MyoD, MyoG, Mymk* and *Mymx*, resulting in increased myoblast proliferation.	Gosselin et al.,[113]
Proteomic screening of total muscle extracts	Diaphragm, 3-month versus 15-month old *mdx-4cv* mouse	Increase in myogenic marker CD34	Gargan et al.,[57]
Multi-omics analysis of myogenesis in dystrophinopathy	Human tissue-derived myoblasts and human induced pluripotent stem cells from Duchenne patients	Establishment of early developmental manifestation of the dystrophic phenotype during myogenesis	Mournetas et al.,[114]
Molecular biological and physiological characterization of *mdx-23* myoblasts	Immortalized *mdx-23* and dystrophin-positive control myoblast cell lines, and primary myoblasts from 2-month old *mdx-23* hindlimb muscles	Myoblasts from *mdx-23* muscle exhibit abnormal calcium-signaling and increased susceptibility to purinergic receptor P2Y-mediated stimulation, causing reduced myoblast motility	Róg et al.,[115,116]
Modelling of dystrophic patient-specific phenotypes in reprogrammed myotubes	Bioengineered dystrophic muscle tissues using culturing and differentiating of MYOD1-directly reprogrammed fibroblasts from Duchenne patients	Determination of cellular and molecular pathogenesis and mechanisms of regeneration in dystrophic myotubes	Barthélémy et al.,[19]
Analysis of dystrophic patient-derived human induced pluripotent stem cells	Skeletal myotubes generated from hiPSCs from 1-8 year old Duchenne patients	Demonstration of pronounced calcium influx in myotubes following electric stimulation for *in vitro* contraction; evaluation of therapeutic strategies	Shoji et al.,[117]; Yoshioka et al.,[118]
Analysis of disturbed bioenergetic metabolism in dystrophic myoblasts	Immortalized *mdx-23* mouse myoblasts and dystrophin-positive controls; e*xtensor digitorum longus* from 2-month old *mdx*/utrophin-/- dKO mice	Mitochondrial dysfunction in dystrophic myoblasts and fused myofibres is associated with reduced oxygen consumption, altered mitochondrial membrane potential and high levels of reactive oxygen species	Onopiuk et al.,[119]; Pant et al.,[120]; Matre et al.,[121]
Analysis of SCs senescence in muscular dystrophy	*Tibialis anterior* and diaphragm primary cell preparations from the dystrophic rat model (DMD rat)	Cellular senescence-mediated exacerbation of muscular dystrophy in association with increased expression of senescence marker genes *CDKN2A*, *p16* and *p19*	Sugihara et al.,[122]

differences in counting approaches and data normalisation in relation to myofibres, myonuclei or muscle area, as recently discussed by Morgan and Partridge.[123,124] Most studies suggest that dystrophin-deficient muscle fibre populations exhibit some degree of SC hyperplasia.[100-104] Increased numbers of PAX7-positive and Dp427-lacking SCs were especially observed in slow-twitching type I fibres as compared to faster twitching type II fibres.[105]

However, an age-related decline in replicative capacity of isolated and dystrophic SCs was shown to occur in young Duchenne patients.[106] Increased SC levels are clearly present in young *mdx-23* mice, which is followed by an age-related decrease in SCs and abnormal Notch signalling,[109] which is a crucial pathway in muscle stem cell development.[125] Notably, depletion of SCs was observed in the severely dystrophic *mdx*/utrophin-/- dKO mouse model of dystrophinopathy, as compared to the milder *mdx-23* phenotype.[110]

Latent regenerative capacity in dystrophic muscles,[16,107,108] is characterized by the retention of a stem cell pool of PAX7-positive SCs with proliferative

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capacity, but incomplete myofiber maturation and lack of preventing skeletal muscle degeneration.[18] Thus, a major pathobiological concept of MuSCs dysfunction in dystrophinopathy is based on the assumption that a disrupted balance of activated SCs exists between symmetric cell division, which is involved in the self-renewal of SCs, and asymmetric cell division, which produces myogenic precursor cells for muscle repair, as diagrammatically outlined in Figure 3.[15] The membrane cytoskeletal protein dystrophin is positioned in the sub-sarcolemmal region in mature myofibres,[126] but also present at relatively high abundance in activated MuSCs and was shown to play a regulatory role in SC polarity and the support of asymmetric cell division.[17,111]

In dystrophin-containing normal SCs, Dp427-M interacts with β1-syntrophin, which in turn binds to the mitogen-activated protein kinase p38γ/MAPK12, and a key regulator of cell polarity, the microtubule affinity regulating serine-threonine kinase MARK2 (PAR1b).[17,59,94] Symmetric division of SCs involves MYF5 (myogenic factor 5) activation by PAX7, depending on CARM1 (coactivator-associated arginine methyltransferase 1), a specific substrate of p38γ/MAPK12. Importantly, the uneven distribution of dystrophin is essential for supporting asymmetric cell division and the initiation of myogenic differentiation in normal skeletal muscle SCs. In contrast, MARK2 expression levels are reduced in dystrophin-lacking SCs, which inhibits the proper delocalization of the cell polarity regulator PARD3 (partitioning defective protein 3) to the opposing side of SCs.[17]

Dysregulation of p38γ/CARM1 signalling occurs in *mdx-23* muscles.[112] Hence, the reduction of asymmetric divisions of SCs that lack dystrophin leads to a drastically lower numbers of myogenic progenitors, which are essential for fibre regeneration. This diminished regenerative capacity due to SC dysfunction in association with Dp427-MARK2-PARD3 dysregulation and a loss of cell polarization,[17] decisively intensifies the overall pathogenesis of dystrophinopathy, which is characterized by highly progressive myonecrosis, chronic inflammation, fat substitution and reactive myofibrosis.

Besides altered patterns of cell division, dystrophic SCs and their activated cell progeny were also shown to be associated with abnormal cellular signalling, metabolic disturbances, defective epigenetic mechanisms, disturbed calcium signalling and mitochondrial dysfunction.[94] Dystrophic myoblasts and fused myofibres exhibit mitochondrial abnormalities, including reduced oxygen consumption, altered mitochondrial membrane potential and high levels of reactive oxygen species.[119-121] Myoblasts from *mdx-23* muscle are characterized by abnormal Ca^{2+}-signalling and an increased susceptibility to purinergic receptor P2Y-mediated stimulation, causing reduced myoblast motility.[115,116] Studies with dystrophic myotubes have revealed abnormal signalling patterns and considerable Ca^{2+}-influx into myocytes following electric stimulation, which can be used as an experimental system for the evaluation of novel therapeutic strategies.[19,117,118] Cellular senescence-mediated exacerbation of muscular dystrophy was established to occur in association with increased expression of senescence marker genes such as *CDKN2A*, *p16* and *p19*.[122] Thus, the inherited muscle wasting disorder DMD fits into the general category of secondarily affected satellite cellopathies,[1,127]

Satellite cells in protected extraocular muscles

In contrast to most skeletal muscle types in the body and their susceptibility to inherited disorders, a divergent subtype is represented by extraocular muscles (EOM) with their unusually high presence of activated stem cells and accompanying levels of extraordinary regenerative capacity.[128] The study of SCs in the EOM cell niche is therefore of considerable biomedical importance, since they represent a naturally protective phenotype of muscular dystrophy.[129] Despite dystrophin deficiency, EOMs retain efficient regenerative capacity.[130,131] A high proliferative rate of specialized regenerative myogenic precursor cell populations seems to play a key role in this protection of EOM morphology and physiological function.[132,133]

EOMs are characterized by a high degree of PITX2 (paired-like homeodomain transcription factor 2) - positive myogenic precursor cells, whereby this transcription factor is involved in the regulation of SC differentiation.[134] Biochemical and proteomic studies confirmed the mild phenotype of dystrophin-lacking EOMs,[135-137] and showed the compensatory upregulation and extra-junctional localization of the autosomal dystrophin homologue utrophin,[138,139] which is highly enriched at the neuromuscular junction in normal skeletal muscle fibres.[140] Hence, the small size of EOMs with relatively low load bearing, a highly efficient Ca^{2+}-extrusion system, extra-junctional utrophin expression and associated rescue of sarcolemmal glycoproteins and/or a significantly higher level of regenerative capacity could explain the milder dystrophic phenotype of this highly specialized type of skeletal muscles.[129,132,141]

Proteomics of satellite cell dysfunction

Although only a limited number of omics-type studies have so far directly focused on the detailed characterization of SCs,[142-144] or the specific role of SCs in dystrophinopathy,[57,113,114] high-throughput systems biological approaches have great potential to further elucidate the role of SC modulation and dysfunction in health and disease. The transcriptomic analysis of *mdx-23* myoblasts has established significant alterations in gene expression patterns, including *MyoD, MyoG, Mymk* and *Mymx*, indicating increased myoblast proliferation.[113] The proteomic screening of total muscle extracts of 3-month versus 15-month old *mdx-4cv* mouse diaphragm preparations has revealed increased levels of

the putative myogenic markers CD34 and cadherin-13 (CDH13, T/H-cadherin).[57] The surface marker protein CD34 was previously identified as a robust SC-linked biomarker.[145-147] A multi-omics analysis of dystrophinopathy was carried out with human tissue-derived myoblasts and human induced pluripotent stem cells (hiPSCs) from Duchenne patients, and established the early developmental manifestation of the dystrophic phenotype during myogenesis.[114]

These initial findings highlight the enormous potential of future proteomics-based studies for the detailed characterization of protein alterations in SCs, focusing specifically on single cell proteomics (SCP).[148-150] Technological approaches using high-throughput sequencing of DNA and RNA in individual cells have contributed enormously to the omics field to date. Proteomic profiling is currently lagging behind these advanced molecular biological screening methods in terms of sensitivity and coverage.[151] However, advancements in the ability to perform SCP is now on a significant upwards trajectory, due in no small part to innovations in sample preparation, chromatography, mass spectrometry hardware and associated workflows.[152] Isobaric tag-based workflows allow for 1000-1500 protein groups to be quantified per cell, with the ability to run dozens of samples daily, demonstrating the high-throughput nature of this approach.[153] Using specific isobaric tandem mass tags (TMT) to label peptides originating from a single cell, multiplexing employing the latest reagents allows multiple individual samples to be combined, often including a carrier channel (100-200 cells) to facilitate peptide identification.[154]

Label-free quantification (LFQ) workflows evaluate each single cell sample individually, with approximately 2000 protein groups identifiable using data dependent acquisition (DDA) modes.[155] However, this approach is more time consuming, reducing the daily number of samples that can be analysed. Many of the studies reporting on SCP and numbers of identifiable protein groups focus on cell lines, for example HeLa cells.[156] Of note, isolated individual muscle fibres contain significantly higher concentrations of protein than HeLa cells, potentially increasing the capability of applying a SCP approach to fragment and identify protein species associated with the myocyte phenotype.[157-159] Recently, Momenzadeh and co-workers,[160] demonstrated the bioanalytical usefulness of this powerful approach, using 15 min run times on a Bruker Tims-TOF SCP instrument combining parallel accumulation serial fragmentation (PASEF) with a data-independent acquisition (DIA) approach, called diaPASEF. Comparing type 1 and 2a myofibres, 94 proteins were found to be statistically different between clusters. This demonstrates the power of this proteomic approach and future applications in muscle physiology and pathophysiology, including muscle regeneration,[161] and the evaluation of novel therapeutic strategies such as myoblast transfer therapy to treat dystrophinopathy.[162]

Therapeutic approaches

Based on the description of major aspects of the molecular and cellular pathogenesis of DMD, a brief overview of novel therapeutic approaches to treat the complex and multi-systems abnormalities of dystrophinopathy is given. A more detailed discussion of impending improvements in pharmacotherapy, stem cell therapy and gene editing is beyond the scope of this review that has focused on muscle degeneration due to dystrophin deficiency. However, a large number of excellent and comprehensive reviews on DMD treatment options have recently been published.[35-37,163] Reports on advances with preclinical and clinical trials and critical discussions of potential issues with biomedical and technical limitations, as well as the clinical advantages of diverse pharmacological, cellular and genetic approaches are available.[38,164-166] The major categories of therapeutic approaches can be divided into (i) muscle stem cell therapy,[167-174] (ii) the pharmacological treatment of complex symptoms associated with the cardio-respiratory syndrome, disturbed ion handling, abnormal cellular signalling, chronic inflammation, disturbed bioenergetics, abnormal cellular growth, dysregulated metabolism and chronic oxidative stress,[175-180] using potentially multi-drug combinations tested in suitable dystrophic animal models,[181] (iii) exon-skipping therapy using antisense molecules,[37,182-187] (iv) CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9) - mediated exon excision and somatic genome editing,[36,188-190] (v) stop codon read-through therapy,[191,192] (vi) vector transfer therapy,[193-195] (vii) targeted dystrophin substitution via its autosomal homologue utrophin,[196-198] (viii) up-regulation of distinct molecular chaperones, such as heat shock proteins, to strengthen the cellular stress response,[199,200] and (ix) electro-stimulation therapy to trigger muscle transformation.[201]

In response to chronic myonecrosis and inflammation, dystrophic skeletal muscles undergo considerable changes in their extracellular matrix environment. Since tissue scarring due to reactive myofibrosis plays a central role in the loss of muscle tissue elasticity and contractility,[78] as well as representing a barrier to many therapeutic approaches including stem cell therapy and gene transfer,[202] anti-fibrosis therapy is of crucial importance in the field of DMD treatment.[81] A drastic decrease in pro-fibrotic proteins using exon-skipping therapy has been suggested as a suitable option to reduce excess scarring of dystrophic muscle tissues.[203]

In conclusion, DMD is characterized by SC dysfunction. Although dystrophin deficiency appears to cause initially SC hyperplasia, myogenic differentiation and muscle regeneration is impaired. A potential mechanism for triggering decreased levels of asymmetric divisions of dystrophic SCs is the reduced expression of crucial binding partners of dystrophin that result in loss of SC polarity. This gives stem cell therapy a central place in

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novel treatment options for improving the regenerative capacity of dystrophic myofibres.

List of acronyms

CARM1 - coactivator-associated arginine methyltransferase 1
COL - collagen
DAMP - damage-associated molecular patterns
DDA - data dependent acquisition
DIA - data-independent acquisition
dKO - double knockout
DMD - Duchenne muscular dystrophy
Dp - dystrophin protein
EOM - extraocular muscle
FAPs - fibro-adipogenic progenitors
FOXO - forkhead box O
hiPSCs - human induced pluripotent stem cells
LFQ - label-free quantification
MAPK12 - mitogen-activated protein kinase 12
MARK2 - microtubule affinity regulating kinase 2
MuSCs - muscle stem cells
MYF5 - myogenic factor 5
MYOD1 - myoblast determination protein 1
MYOG - muscle-specific transcription factor myogenin
P2Y - purinoceptor 2
PARD3 - partitioning defective protein 3
PASEF - parallel accumulation serial fragmentation
PAX7 - paired box 7 transcription factor
PITX2 - paired-like homeodomain transcription factor 2
SC - satellite cell
SCP - single cell proteomics
TGF - transforming growth factor
TMT - tandem mass tags
TNF - tumour necrosis factor

Contributions of Authors

PD, DS, and KO were involved in the conceptualization and initiation of this review project, as well as the design of the literature search strategy. All authors were involved in the writing and final editing of the typescript. All authors read and approved the final edited typescript.

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The authors declare no competing interests.

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References

1. Ganassi M, Zammit PS. Involvement of muscle satellite cell dysfunction in neuromuscular disorders: Expanding the portfolio of satellite cell-opathies. Eur J Transl Myol. 2022 Mar 18;32(1):10064. doi: 10.4081/ejtm.2022.10064. PMID: 35302338; PMCID: PMC8992676.
2. Mauro A. Satellite cell of skeletal muscle fibers. J Biophys Biochem Cytol. 1961 Feb;9(2):493-5. doi: 10.1083/jcb.9.2.493. PMID: 13768451; PMCID: PMC2225012.
3. Katz B. The terminations of the afferent nerve fibre in the muscle spindle of the frog. Philos Trans R Soc Lond (Biol) 1961;243:221–240. doi: 10.1098/rstb.1961.0001.
4. Scharner J, Zammit PS. The muscle satellite cell at 50: the formative years. Skelet Muscle. 2011 Aug 17;1(1):28. doi: 10.1186/2044-5040-1-28. PMID: 21849021; PMCID: PMC3177780.
5. Yablonka-Reuveni Z. The skeletal muscle satellite cell: still young and fascinating at 50. J Histochem Cytochem. 2011 Dec;59(12):1041-59. doi: 10.1369/0022155411426780. PMID: 22147605; PMCID: PMC3283088.
6. Morgan JE, Partridge TA. Muscle satellite cells. Int J Biochem Cell Biol. 2003 Aug;35(8):1151-6. doi: 10.1016/s1357-2725(03)00042-6. PMID: 12757751.
7. Zammit PS, Partridge TA, Yablonka-Reuveni Z. The skeletal muscle satellite cell: the stem cell that came in from the cold. J Histochem Cytochem. 2006 Nov;54(11):1177-91. doi: 10.1369/jhc.6R6995.2006. Epub 2006 Aug 9. PMID: 16899758.
8. Engquist EN, Zammit PS. The Satellite Cell at 60: The Foundation Years. J Neuromuscul Dis. 2021;8(s2):S183-S203. doi: 10.3233/JND-210705. PMID: 34459412; PMCID: PMC8673500.
9. Murach KA, Fry CS, Dupont-Versteegden EE, McCarthy JJ, Peterson CA. Fusion and beyond: Satellite cell contributions to loading-induced skeletal muscle adaptation. FASEB J. 2021 Oct;35(10):e21893. doi: 10.1096/fj.202101096R. PMID: 34480776; PMCID: PMC9293230.

10. Sousa-Victor P, García-Prat L, Muñoz-Cánoves P. Control of satellite cell function in muscle regeneration and its disruption in ageing. Nat Rev Mol Cell Biol. 2022 Mar;23(3):204-226. doi: 10.1038/s41580-021-00421-2. Epub 2021 Oct 18. PMID: 34663964.
11. Pang KT, Loo LSW, Chia S, Ong FYT, Yu H, Walsh I. Insight into muscle stem cell regeneration and mechanobiology. Stem Cell Res Ther. 2023 May 12;14(1):129. doi: 10.1186/s13287-023-03363-y. PMID: 37173707; PMCID: PMC10176686.
12. Mussini I, Favaro G, Carraro U. Maturation, dystrophic changes and the continuous production of fibers in skeletal muscle regenerating in the absence of nerve. J Neuropathol Exp Neurol. 1987 May;46(3):315-31. doi: 10.1097/00005072-198705000-00007. PMID: 3559631.
13. Carraro U, Boncompagni S, Gobbo V, Rossini K, Zampieri S, Mosole S, Ravara B, Nori A, Stramare R, Ambrosio F, Piccione F, Masiero S, Vindigni V, Gargiulo P, Protasi F, Kern H, Pond A, Marcante A. Persistent Muscle Fiber Regeneration in Long Term Denervation. Past, Present, Future. Eur J Transl Myol. 2015 Mar 11;25(2):4832. doi: 10.4081/ejtm.2015.4832. PMID: 26913148; PMCID: PMC4383182.
14. Wang YX, Rudnicki MA. Satellite cells, the engines of muscle repair. Nat Rev Mol Cell Biol. 2011 Dec 21;13(2):127-33. doi: 10.1038/nrm3265. PMID: 22186952.
15. Chang NC, Chevalier FP, Rudnicki MA. Satellite Cells in Muscular Dystrophy - Lost in Polarity. Trends Mol Med. 2016 Jun;22(6):479-496. doi: 10.1016/j.molmed.2016.04.002. Epub 2016 May 5. PMID: 27161598; PMCID: PMC4885782.
16. Yablonka-Reuveni Z, Anderson JE. Satellite cells from dystrophic (mdx) mice display accelerated differentiation in primary cultures and in isolated myofibers. Dev Dyn. 2006 Jan;235(1):203-12. doi: 10.1002/dvdy.20602. PMID: 16258933.
17. Dumont NA, Wang YX, von Maltzahn J, Pasut A, Bentzinger CF, Brun CE, Rudnicki MA. Dystrophin expression in muscle stem cells regulates their polarity and asymmetric division. Nat Med. 2015 Dec;21(12):1455-63. doi: 10.1038/nm.3990. Epub 2015 Nov 16. PMID: 26569381; PMCID: PMC4839960.
18. Ribeiro AF Jr, Souza LS, Almeida CF, Ishiba R, Fernandes SA, Guerrieri DA, Santos ALF, Onofre-Oliveira PCG, Vainzof M. Muscle satellite cells and impaired late stage regeneration in different murine models for muscular dystrophies. Sci Rep. 2019 Aug 14;9(1):11842. doi: 10.1038/s41598-019-48156-7. PMID: 31413358; PMCID: PMC6694188.
19. Barthélémy F, Santoso JW, Rabichow L, Jin R, Little I, Nelson SF, McCain ML, Miceli MC. Modeling Patient-Specific Muscular Dystrophy Phenotypes and Therapeutic Responses in Reprogrammed Myotubes Engineered on Micromolded Gelatin Hydrogels. Front Cell Dev Biol. 2022 Apr 6;10:830415. doi: 10.3389/fcell.2022.830415. PMID: 35465312; PMCID: PMC9020228.
20. Rosenberg AS, Puig M, Nagaraju K, Hoffman EP, Villalta SA, Rao VA, Wakefield LM, Woodcock J. Immune-mediated pathology in Duchenne muscular dystrophy. Sci Transl Med. 2015 Aug 5;7(299):299rv4. doi: 10.1126/scitranslmed.aaa7322. PMID: 26246170; PMCID: PMC5951380.
21. Ohlendieck K, Swandulla D. Molekulare Pathogenese der Fibrose bei Muskeldystrophie vom Typ Duchenne [Molecular pathogenesis of Duchenne muscular dystrophy-related fibrosis]. Pathologe. 2017 Feb;38(1):21-29. German. doi: 10.1007/s00292-017-0265-1. PMID: 28097378.
22. Bez Batti Angulski A, Hosny N, Cohen H, Martin AA, Hahn D, Bauer J, Metzger JM. Duchenne muscular dystrophy: disease mechanism and therapeutic strategies. Front Physiol. 2023 Jun 26;14:1183101. doi: 10.3389/fphys.2023.1183101. PMID: 37435300; PMCID: PMC10330733.
23. Duan D, Goemans N, Takeda S, Mercuri E, Aartsma-Rus A. Duchenne muscular dystrophy. Nat Rev Dis Primers. 2021 Feb 18;7(1):13. doi: 10.1038/s41572-021-00248-3. PMID: 33602943.
24. Hoffman EP. The discovery of dystrophin, the protein product of the Duchenne muscular dystrophy gene. FEBS J. 2020 Sep;287(18):3879-3887. doi: 10.1111/febs.15466. Epub 2020 Jul 21. PMID: 32608079; PMCID: PMC7540009.
25. Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. Lancet Neurol. 2003 Dec;2(12):731-40. doi: 10.1016/s1474-4422(03)00585-4. PMID: 14636778.
26. Ferlini A, Neri M, Gualandi F. The medical genetics of dystrophinopathies: molecular genetic diagnosis and its impact on clinical practice. Neuromuscul Disord. 2013 Jan;23(1):4-14. doi: 10.1016/j.nmd.2012.09.002. Epub 2012 Oct 30. PMID: 23116935.
27. Gaina G, Vossen RHAM, Manole E, Plesca DA, Ionica E. Combining Protein Expression and Molecular Data Improves Mutation Characterization of Dystrophinopathies. Front Neurol. 2021 Dec 7;12:718396. doi: 10.3389/fneur.2021.718396. PMID: 34950096; PMCID: PMC8689184.
28. Bello L, Hoffman EP, Pegoraro E. Is it time for genetic modifiers to predict prognosis in Duchenne muscular dystrophy? Nat Rev Neurol. 2023 Jul;19(7):410-423. doi: 10.1038/s41582-023-00823-0. Epub 2023 Jun 12. PMID: 37308617.

29. Schultz TI, Raucci FJ Jr, Salloum FN. Cardiovascular Disease in Duchenne Muscular Dystrophy: Overview and Insight Into Novel Therapeutic Targets. JACC Basic Transl Sci. 2022 Mar 9;7(6):608-625. doi: 10.1016/j.jacbts.2021.11.004. PMID: 35818510; PMCID: PMC9270569.
30. Pascual-Morena C, Cavero-Redondo I, Martínez-Vizcaíno V, Sequí-Domínguez I, Fernández-Bravo-Rodrigo J, Jiménez-López E. Dystrophin Genotype and Risk of Neuropsychiatric Disorders in Dystrophinopathies: A Systematic Review and Meta-Analysis. J Neuromuscul Dis. 2023;10(2):159-172. doi: 10.3233/JND-221586. PMID: 36565132; PMCID: PMC10041431.
31. Ohlendieck K, Swandulla D. Complexity of skeletal muscle degeneration: multi-systems pathophysiology and organ crosstalk in dystrophinopathy. Pflugers Arch. 2021 Dec;473(12):1813-1839. doi: 10.1007/s00424-021-02623-1. Epub 2021 Sep 22. PMID: 34553265; PMCID: PMC8599371.
32. Murphy S, Ohlendieck K. The biochemical and mass spectrometric profiling of the dystrophin complexome from skeletal muscle. Comput Struct Biotechnol J. 2015 Nov 26;14:20-7. doi: 10.1016/j.csbj.2015.11.002. PMID: 26793286; PMCID: PMC4688399.
33. Ohlendieck K. Towards an understanding of the dystrophin-glycoprotein complex: linkage between the extracellular matrix and the membrane cytoskeleton in muscle fibers. Eur J Cell Biol. 1996 Jan;69(1):1-10. PMID: 8825019.
34. Dowling P, Gargan S, Murphy S, Zweyer M, Sabir H, Swandulla D, Ohlendieck K. The Dystrophin Node as Integrator of Cytoskeletal Organization, Lateral Force Transmission, Fiber Stability and Cellular Signaling in Skeletal Muscle. Proteomes. 2021 Feb 2;9(1):9. doi: 10.3390/proteomes9010009. PMID: 33540575; PMCID: PMC7931087.
35. Partridge TA. Impending therapies for Duchenne muscular dystrophy. Curr Opin Neurol. 2011 Oct;24(5):415-22. doi: 10.1097/WCO.0b013e32834aa3f1. PMID: 21892079.
36. Chemello F, Olson EN, Bassel-Duby R. CRISPR-Editing Therapy for Duchenne Muscular Dystrophy. Hum Gene Ther. 2023 May;34(9-10):379-387. doi: 10.1089/hum.2023.053. PMID: 37060194; PMCID: PMC10210224.
37. Mercuri E, Seferian AM, Servais L, Deconinck N, Stevenson H, Ni X, Zhang W, East L, Yonren S, Muntoni F; 4658-102 Study Group. Safety, tolerability and pharmacokinetics of eteplirsen in young boys aged 6-48 months with Duchenne muscular dystrophy amenable to exon 51 skipping. Neuromuscul Disord. 2023 Jun;33(6):476-483. doi: 10.1016/j.nmd.2023.03.008. Epub 2023 Mar 24. PMID: 37207382.
38. Duan D. Duchenne Muscular Dystrophy Gene Therapy in 2023: Status, Perspective, and Beyond. Hum Gene Ther. 2023 May;34(9-10):345-349. doi: 10.1089/hum.2023.29242.ddu. PMID: 37219994; PMCID: PMC10325806.
39. Dowling P, Murphy S, Zweyer M, Raucamp M, Swandulla D, Ohlendieck K. Emerging proteomic biomarkers of X-linked muscular dystrophy. Expert Rev Mol Diagn. 2019 Aug;19(8):739-755. doi: 10.1080/14737159.2019.1648214. Epub 2019 Aug 2. PMID: 31359811.
40. Al-Khalili Szigyarto C. Duchenne Muscular Dystrophy: recent advances in protein biomarkers and the clinical application. Expert Rev Proteomics. 2020 May;17(5):365-375. doi: 10.1080/14789450.2020.1773806. PMID: 32713262.
41. Fortunato F, Ferlini A. Biomarkers in Duchenne Muscular Dystrophy: Current Status and Future Directions. J Neuromuscul Dis. 2023 Jul 29. doi: 10.3233/JND-221666. Epub ahead of print. PMID: 37545256.
42. Ervasti JM, Ohlendieck K, Kahl SD, Gaver MG, Campbell KP. Deficiency of a glycoprotein component of the dystrophin complex in dystrophic muscle. Nature. 1990 May 24;345(6273):315-9. doi: 10.1038/345315a0. PMID: 2188135.
43. Ohlendieck K, Campbell KP. Dystrophin-associated proteins are greatly reduced in skeletal muscle from mdx mice. J Cell Biol. 1991 Dec;115(6):1685-94. doi: 10.1083/jcb.115.6.1685. PMID: 1757468; PMCID: PMC2289197.
44. Ohlendieck K, Matsumura K, Ionasescu VV, Towbin JA, Bosch EP, Weinstein SL, Sernett SW, Campbell KP. Duchenne muscular dystrophy: deficiency of dystrophin-associated proteins in the sarcolemma. Neurology. 1993 Apr;43(4):795-800. doi: 10.1212/wnl.43.4.795. PMID: 8469343.
45. Murphy S, Zweyer M, Henry M, Meleady P, Mundegar RR, Swandulla D, Ohlendieck K. Proteomic analysis of the sarcolemma-enriched fraction from dystrophic mdx-4cv skeletal muscle. J Proteomics. 2019 Jan 16;191:212-227. doi: 10.1016/j.jprot.2018.01.015. Epub 2018 Feb 2. PMID: 29408692.
46. Zabłocka B, Górecki DC, Zabłocki K. Disrupted Calcium Homeostasis in Duchenne Muscular Dystrophy: A Common Mechanism behind Diverse Consequences. Int J Mol Sci. 2021 Oct 13;22(20):11040. doi: 10.3390/ijms222011040. PMID: 34681707; PMCID: PMC8537421.
47. Culligan K, Banville N, Dowling P, Ohlendieck K. Drastic reduction of calsequestrin-like proteins and impaired calcium binding in dystrophic mdx muscle. J Appl Physiol (1985). 2002 Feb;92(2):435-45. doi:

10.1152/japplphysiol.00903.2001. PMID: 11796649.

48. Dowling P, Doran P, Ohlendieck K. Drastic reduction of sarcalumenin in Dp427 (dystrophin of 427 kDa)-deficient fibres indicates that abnormal calcium handling plays a key role in muscular dystrophy. Biochem J. 2004 Apr 15;379(Pt 2):479-88. doi: 10.1042/BJ20031311. PMID: 14678011; PMCID: PMC1224066.
49. Dowling P, Gargan S, Swandulla D, Ohlendieck K. Proteomic profiling of impaired excitation-contraction coupling and abnormal calcium handling in muscular dystrophy. Proteomics. 2022 Dec;22(23-24):e2200003. doi: 10.1002/pmic.202200003. Epub 2022 Aug 8. PMID: 35902360; PMCID: PMC10078611.
50. Partridge TA. The mdx mouse model as a surrogate for Duchenne muscular dystrophy. FEBS J. 2013 Sep;280(17):4177-86. doi: 10.1111/febs.12267. Epub 2013 Apr 22. PMID: 23551987; PMCID: PMC4147949.
51. Cassano M, Berardi E, Crippa S, Toelen J, Barthelemy I, Micheletti R, Chuah M, Vandendriessche T, Debyser Z, Blot S, Sampaolesi M. Alteration of cardiac progenitor cell potency in GRMD dogs. Cell Transplant. 2012;21(9):1945-67. doi: 10.3727/096368912X638919. Epub 2012 Apr 10. PMID: 22513051.
52. Echigoya Y, Trieu N, Duddy W, Moulton HM, Yin H, Partridge TA, Hoffman EP, Kornegay JN, Rohret FA, Rogers CS, Yokota T. A Dystrophin Exon-52 Deleted Miniature Pig Model of Duchenne Muscular Dystrophy and Evaluation of Exon Skipping. Int J Mol Sci. 2021 Dec 2;22(23):13065. doi: 10.3390/ijms222313065. PMID: 34884867; PMCID: PMC8657897.
53. Wilson K, Faelan C, Patterson-Kane JC, Rudmann DG, Moore SA, Frank D, Charleston J, Tinsley J, Young GD, Milici AJ. Duchenne and Becker Muscular Dystrophies: A Review of Animal Models, Clinical End Points, and Biomarker Quantification. Toxicol Pathol. 2017 Oct;45(7):961-976. doi: 10.1177/0192623317734823. Epub 2017 Oct 3. PMID: 28974147; PMCID: PMC5788182.
54. Grounds MD, Terrill JR, Al-Mshhdani BA, Duong MN, Radley-Crabb HG, Arthur PG. Biomarkers for Duchenne muscular dystrophy: myonecrosis, inflammation and oxidative stress. Dis Model Mech. 2020 Mar 2;13(2):dmm043638. doi: 10.1242/dmm.043638. PMID: 32224496; PMCID: PMC7063669.
55. Mázala DAG, Hindupur R, Moon YJ, Shaikh F, Gamu IH, Alladi D, Panci G, Weiss-Gayet M, Chazaud B, Partridge TA, Novak JS, Jaiswal JK. Altered muscle niche contributes to myogenic deficit in the D2-mdx model of severe DMD. Cell Death Discov. 2023 Jul 4;9(1):224. doi: 10.1038/s41420-023-01503-0. PMID: 37402716; PMCID: PMC10319851.
56. Mázala DA, Novak JS, Hogarth MW, Nearing M, Adusumalli P, Tully CB, Habib NF, Gordish-Dressman H, Chen YW, Jaiswal JK, Partridge TA. TGF-β-driven muscle degeneration and failed regeneration underlie disease onset in a DMD mouse model. JCI Insight. 2020 Mar 26;5(6):e135703. doi: 10.1172/jci.insight.135703. PMID: 32213706; PMCID: PMC7213798.
57. Gargan S, Dowling P, Zweyer M, Henry M, Meleady P, Swandulla D, Ohlendieck K. Proteomic Identification of Markers of Membrane Repair, Regeneration and Fibrosis in the Aged and Dystrophic Diaphragm. Life (Basel). 2022 Oct 22;12(11):1679. doi: 10.3390/life12111679. PMID: 36362832; PMCID: PMC9696191.
58. Zweyer M, Sabir H, Dowling P, Gargan S, Murphy S, Swandulla D, Ohlendieck K. Histopathology of Duchenne muscular dystrophy in correlation with changes in proteomic biomarkers. Histol Histopathol. 2022 Feb;37(2):101-116. doi: 10.14670/HH-18-403. Epub 2021 Dec 7. PMID: 34873679.
59. Starosta A, Konieczny P. Therapeutic aspects of cell signaling and communication in Duchenne muscular dystrophy. Cell Mol Life Sci. 2021 Jun;78(11):4867-4891. doi: 10.1007/s00018-021-03821-x. Epub 2021 Apr 7. PMID: 33825942; PMCID: PMC8233280.
60. Tidball JG, Welc SS, Wehling-Henricks M. Immunobiology of Inherited Muscular Dystrophies. Compr Physiol. 2018 Sep 14;8(4):1313-1356. doi: 10.1002/cphy.c170052. PMID: 30215857; PMCID: PMC7769418.
61. Bonomo AC, Pinto-Mariz F, Riederer I, Benjamim CF, Butler-Browne G, Mouly V, Savino W. Crosstalk Between Innate and T Cell Adaptive Immunity With(in) the Muscle. Front Physiol. 2020 Sep 18;11:573347. doi: 10.3389/fphys.2020.573347. PMID: 33071827; PMCID: PMC7531250.
62. Spencer MJ, Montecino-Rodriguez E, Dorshkind K, Tidball JG. Helper (CD4(+)) and cytotoxic (CD8(+)) T cells promote the pathology of dystrophin-deficient muscle. Clin Immunol. 2001 Feb;98(2):235-43. doi: 10.1006/clim.2000.4966. PMID: 11161980.
63. Mojumdar K, Liang F, Giordano C, Lemaire C, Danialou G, Okazaki T, Bourdon J, Rafei M, Galipeau J, Divangahi M, Petrof BJ. Inflammatory monocytes promote progression of Duchenne muscular dystrophy and can be therapeutically targeted via CCR2. EMBO Mol Med. 2014 Nov;6(11):1476-92. doi: 10.15252/emmm.201403967. PMID: 25312642; PMCID: PMC4237472.

64. Dowling P, Gargan S, Zweyer M, Henry M, Meleady P, Swandulla D, Ohlendieck K. Proteome-wide Changes in the mdx-4cv Spleen due to Pathophysiological Cross Talk with Dystrophin-Deficient Skeletal Muscle. iScience. 2020 Aug 26;23(9):101500. doi: 10.1016/j.isci.2020.101500. Epub ahead of print. PMID: 32916630; PMCID: PMC7490529.
65. Dowling P, Gargan S, Zweyer M, Henry M, Meleady P, Swandulla D, Ohlendieck K. Protocol for the Bottom-Up Proteomic Analysis of Mouse Spleen. STAR Protoc. 2020 Dec 3;1(3):100196. doi: 10.1016/j.xpro.2020.100196. PMID: 33377090; PMCID: PMC7757555.
66. Rizzo G, Di Maggio R, Benedetti A, Morroni J, Bouche M, Lozanoska-Ochser B. Splenic Ly6Chi monocytes are critical players in dystrophic muscle injury and repair. JCI Insight. 2020 Jan 30;5(2):e130807. doi: 10.1172/jci.insight.130807. PMID: 31874104; PMCID: PMC7098719.
67. Strizova Z, Benesova I, Bartolini R, Novysedlak R, Cecrdlova E, Foley LK, Striz I. M1/M2 macrophages and their overlaps - myth or reality? Clin Sci (Lond). 2023 Aug 14;137(15):1067-1093. doi: 10.1042/CS20220531. PMID: 37530555; PMCID: PMC10407193.
68. Spencer MJ, Tidball JG. Do immune cells promote the pathology of dystrophin-deficient myopathies? Neuromuscul Disord. 2001 Sep;11(6-7):556-64. doi: 10.1016/s0960-8966(01)00198-5. PMID: 11525885.
69. Malecova B, Gatto S, Etxaniz U, Passafaro M, Cortez A, Nicoletti C, Giordani L, Torcinaro A, De Bardi M, Bicciato S, De Santa F, Madaro L, Puri PL. Dynamics of cellular states of fibro-adipogenic progenitors during myogenesis and muscular dystrophy. Nat Commun. 2018 Sep 10;9(1):3670. doi: 10.1038/s41467-018-06068-6. PMID: 30202063; PMCID: PMC6131350.
70. Negroni E, Kondili M, Muraine L, Bensalah M, Butler-Browne GS, Mouly V, Bigot A, Trollet C. Muscle fibro-adipogenic progenitors from a single-cell perspective: Focus on their "virtual" secretome. Front Cell Dev Biol. 2022 Sep 19;10:952041. doi: 10.3389/fcell.2022.952041. PMID: 36200044; PMCID: PMC9527288.
71. Biferali B, Proietti D, Mozzetta C, Madaro L. Fibro-Adipogenic Progenitors Cross-Talk in Skeletal Muscle: The Social Network. Front Physiol. 2019 Aug 21;10:1074. doi: 10.3389/fphys.2019.01074. PMID: 31496956; PMCID: PMC6713247.
72. Molina T, Fabre P, Dumont NA. Fibro-adipogenic progenitors in skeletal muscle homeostasis, regeneration and diseases. Open Biol. 2021 Dec;11(12):210110. doi: 10.1098/rsob.210110. Epub 2021 Dec 8. PMID: 34875199; PMCID: PMC8651418.
73. Theret M, Rossi FMV, Contreras O. Evolving Roles of Muscle-Resident Fibro-Adipogenic Progenitors in Health, Regeneration, Neuromuscular Disorders, and Aging. Front Physiol. 2021 Apr 20;12:673404. doi: 10.3389/fphys.2021.673404. PMID: 33959042; PMCID: PMC8093402.
74. Mojumdar K, Giordano C, Lemaire C, Liang F, Divangahi M, Qureshi ST, Petrof BJ. Divergent impact of Toll-like receptor 2 deficiency on repair mechanisms in healthy muscle versus Duchenne muscular dystrophy. J Pathol. 2016 May;239(1):10-22. doi: 10.1002/path.4689. Epub 2016 Mar 16. PMID: 26800321.
75. Bello L, Pegoraro E. The "Usual Suspects": Genes for Inflammation, Fibrosis, Regeneration, and Muscle Strength Modify Duchenne Muscular Dystrophy. J Clin Med. 2019 May 10;8(5):649. doi: 10.3390/jcm8050649. PMID: 31083420; PMCID: PMC6571893.
76. Giuliani G, Rosina M, Reggio A. Signaling pathways regulating the fate of fibro/adipogenic progenitors (FAPs) in skeletal muscle regeneration and disease. FEBS J. 2022 Nov;289(21):6484-6517. doi: 10.1111/febs.16080. Epub 2021 Jul 6. PMID: 34143565.
77. Desguerre I, Mayer M, Leturcq F, Barbet JP, Gherardi RK, Christov C. Endomysial fibrosis in Duchenne muscular dystrophy: a marker of poor outcome associated with macrophage alternative activation. J Neuropathol Exp Neurol. 2009 Jul;68(7):762-73. doi: 10.1097/NEN.0b013e3181aa31c2. PMID: 19535995.
78. Klingler W, Jurkat-Rott K, Lehmann-Horn F, Schleip R. The role of fibrosis in Duchenne muscular dystrophy. Acta Myol. 2012 Dec;31(3):184-95. PMID: 23620650; PMCID: PMC3631802.
79. Dowling P, Gargan S, Zweyer M, Swandulla D, Ohlendieck K. Extracellular Matrix Proteomics: The mdx-4cv Mouse Diaphragm as a Surrogate for Studying Myofibrosis in Dystrophinopathy. Biomolecules. 2023 Jul 12;13(7):1108. doi: 10.3390/biom13071108. PMID: 37509144; PMCID: PMC10377647.
80. Holland A, Dowling P, Meleady P, Henry M, Zweyer M, Mundegar RR, Swandulla D, Ohlendieck K. Label-free mass spectrometric analysis of the mdx-4cv diaphragm identifies the matricellular protein periostin as a potential factor involved in dystrophinopathy-related fibrosis. Proteomics. 2015 Jul;15(13):2318-31. doi: 10.1002/pmic.201400471. Epub 2015 Apr 1. PMID: 25737063.
81. Muraine L, Bensalah M, Butler-Browne G, Bigot A, Trollet C, Mouly V, Negroni E. Update on anti-fibrotic pharmacotherapies in skeletal muscle disease. Curr Opin Pharmacol. 2023

Feb;68:102332. doi: 10.1016/j.coph.2022.102332. Epub 2022 Dec 23. PMID: 36566666.
82. Camps J, Breuls N, Sifrim A, Giarratana N, Corvelyn M, Danti L, Grosemans H, Vanuytven S, Thiry I, Belicchi M, Meregalli M, Platko K, MacDonald ME, Austin RC, Gijsbers R, Cossu G, Torrente Y, Voet T, Sampaolesi M. Interstitial Cell Remodeling Promotes Aberrant Adipogenesis in Dystrophic Muscles. Cell Rep. 2020 May 5;31(5):107597. doi: 10.1016/j.celrep.2020.107597. PMID: 32375047.
83. Veeger TTJ, van Zwet EW, Al Mohamad D, Naarding KJ, van de Velde NM, Hooijmans MT, Webb AG, Niks EH, de Groot JH, Kan HE. Muscle architecture is associated with muscle fat replacement in Duchenne and Becker muscular dystrophies. Muscle Nerve. 2021 Nov;64(5):576-584. doi: 10.1002/mus.27399. Epub 2021 Aug 25. PMID: 34383334; PMCID: PMC9290788.
84. Huysmans L, De Wel B, Claeys KG, Maes F. Automated MRI quantification of volumetric per-muscle fat fractions in the proximal leg of patients with muscular dystrophies. Front Neurol. 2023 May 24;14:1200727. doi: 10.3389/fneur.2023.1200727. PMID: 37292137; PMCID: PMC10244517.
85. Hooijmans MT, Niks EH, Burakiewicz J, Anastasopoulos C, van den Berg SI, van Zwet E, Webb AG, Verschuuren JJGM, Kan HE. Non-uniform muscle fat replacement along the proximodistal axis in Duchenne muscular dystrophy. Neuromuscul Disord. 2017 May;27(5):458-464. doi: 10.1016/j.nmd.2017.02.009. Epub 2017 Feb 21. PMID: 28302391.
86. Morgan JE, Zammit PS. Direct effects of the pathogenic mutation on satellite cell function in muscular dystrophy. Exp Cell Res. 2010 Nov 1;316(18):3100-8. doi: 10.1016/j.yexcr.2010.05.014. Epub 2010 May 28. PMID: 20546725.
87. Buckingham M, Relaix F. PAX3 and PAX7 as upstream regulators of myogenesis. Semin Cell Dev Biol. 2015 Aug;44:115-25. doi: 10.1016/j.semcdb.2015.09.017. Epub 2015 Sep 28. PMID: 26424495.
88. Zammit PS. Function of the myogenic regulatory factors Myf5, MyoD, Myogenin and MRF4 in skeletal muscle, satellite cells and regenerative myogenesis. Semin Cell Dev Biol. 2017 Dec;72:19-32. doi: 10.1016/j.semcdb.2017.11.011. Epub 2017 Nov 15. PMID: 29127046.
89. Ganassi M, Badodi S, Ortuste Quiroga HP, Zammit PS, Hinits Y, Hughes SM. Myogenin promotes myocyte fusion to balance fibre number and size. Nat Commun. 2018 Oct 12;9(1):4232. doi: 10.1038/s41467-018-06583-6. PMID: 30315160; PMCID: PMC6185967.
90. Chang NC, Rudnicki MA. Satellite cells: the architects of skeletal muscle. Curr Top Dev Biol. 2014;107:161-81. doi: 10.1016/B978-0-12-416022-4.00006-8. PMID: 24439806.
91. Rudnicki MA, Le Grand F, McKinnell I, Kuang S. The molecular regulation of muscle stem cell function. Cold Spring Harb Symp Quant Biol. 2008;73:323-31. doi: 10.1101/sqb.2008.73.064. Epub 2009 Mar 27. PMID: 19329572.
92. Ganassi M, Badodi S, Wanders K, Zammit PS, Hughes SM. Myogenin is an essential regulator of adult myofibre growth and muscle stem cell homeostasis. Elife. 2020 Oct 1;9:e60445. doi: 10.7554/eLife.60445. PMID: 33001028; PMCID: PMC7599067.
93. Massenet J, Gardner E, Chazaud B, Dilworth FJ. Epigenetic regulation of satellite cell fate during skeletal muscle regeneration. Skelet Muscle. 2021 Jan 11;11(1):4. doi: 10.1186/s13395-020-00259-w. PMID: 33431060; PMCID: PMC7798257.
94. Kodippili K, Rudnicki MA. Satellite cell contribution to disease pathology in Duchenne muscular dystrophy. Front Physiol. 2023 May 30;14:1180980. doi: 10.3389/fphys.2023.1180980. PMID: 37324396; PMCID: PMC10266354.
95. Kahn RE, Dayanidhi S, Lacham-Kaplan O, Hawley JA. Molecular clocks, satellite cells, and skeletal muscle regeneration. Am J Physiol Cell Physiol. 2023 Jun 1;324(6):C1332-C1340. doi: 10.1152/ajpcell.00073.2023. Epub 2023 May 15. PMID: 37184229.
96. Johnson AL, Kamal M, Parise G. The Role of Supporting Cell Populations in Satellite Cell Mediated Muscle Repair. Cells. 2023 Jul 30;12(15):1968. doi: 10.3390/cells12151968. PMID: 37566047.
97. Yablonka-Reuveni Z, Lepper C. New Insight into a Classic Stem Cell: the Satellite Cell may Communicate with the Muscle Fiber via Extracellular Vesicles-A Perspective on "Fusion-Independent Satellite Cell Communication to Muscle Fibers During Load-Induced Hypertrophy". Function (Oxf). 2020 Sep 3;1(2):zqaa015. doi: 10.1093/function/zqaa015. PMID: 35330641; PMCID: PMC8788824.
98. Rugowska A, Starosta A, Konieczny P. Epigenetic modifications in muscle regeneration and progression of Duchenne muscular dystrophy. Clin Epigenetics. 2021 Jan 19;13(1):13. doi: 10.1186/s13148-021-01001-z. PMID: 33468200; PMCID: PMC7814631.
99. Heslop L, Morgan JE, Partridge TA. Evidence for a myogenic stem cell that is exhausted in dystrophic muscle. J Cell Sci. 2000 Jun;113 (Pt 12):2299-308. doi: 10.1242/jcs.113.12.2299. PMID: 10825301.
100. Wakayama Y, Schotland DL, Bonilla E, Orecchio E. Quantitative ultrastructural study of muscle satellite cells in Duchenne dystrophy. Neurology.

1979 Mar;29(3):401-7. doi: 10.1212/wnl.29.3.401. PMID: 571989.
101. Ishimoto S, Goto I, Ohta M, Kuroiwa Y. A quantitative study of the muscle satellite cells in various neuromuscular disorders. J Neurol Sci. 1983 Dec;62(1-3):303-14. doi: 10.1016/0022-510x(83)90207-1. PMID: 6668477.
102. Watkins SC, Cullen MJ. A quantitative comparison of satellite cell ultrastructure in Duchenne muscular dystrophy, polymyositis, and normal controls. Muscle Nerve. 1986 Oct;9(8):724-30. doi: 10.1002/mus.880090808. PMID: 3785283.
103. Watkins SC, Cullen MJ. A quantitative study of myonuclear and satellite cell nuclear size in Duchenne's muscular dystrophy, polymyositis and normal human skeletal muscle. Anat Rec. 1988 Sep;222(1):6-11. doi: 10.1002/ar.1092220103. PMID: 3189887.
104. Kottlors M, Kirschner J. Elevated satellite cell number in Duchenne muscular dystrophy. Cell Tissue Res. 2010 Jun;340(3):541-8. doi: 10.1007/s00441-010-0976-6. Epub 2010 May 15. PMID: 20467789.
105. Bankolé LC, Feasson L, Ponsot E, Kadi F. Fibre type-specific satellite cell content in two models of muscle disease. Histopathology. 2013 Dec;63(6):826-32. doi: 10.1111/his.12231. Epub 2013 Sep 20. PMID: 24111647.
106. Webster C, Blau HM. Accelerated age-related decline in replicative life-span of Duchenne muscular dystrophy myoblasts: implications for cell and gene therapy. Somat Cell Mol Genet. 1990 Nov;16(6):557-65. doi: 10.1007/BF01233096. PMID: 2267630.
107. Boldrin L, Zammit PS, Morgan JE. Satellite cells from dystrophic muscle retain regenerative capacity. Stem Cell Res. 2015 Jan;14(1):20-9. doi: 10.1016/j.scr.2014.10.007. Epub 2014 Nov 1. PMID: 25460248; PMCID: PMC4305370.
108. Matecki S, Guibinga GH, Petrof BJ. Regenerative capacity of the dystrophic (mdx) diaphragm after induced injury. Am J Physiol Regul Integr Comp Physiol. 2004 Oct;287(4):R961-8. doi: 10.1152/ajpregu.00146.2004. Epub 2004 Jun 10. PMID: 15191902.
109. Jiang C, Wen Y, Kuroda K, Hannon K, Rudnicki MA, Kuang S. Notch signaling deficiency underlies age-dependent depletion of satellite cells in muscular dystrophy. Dis Model Mech. 2014 Aug;7(8):997-1004. doi: 10.1242/dmm.015917. Epub 2014 Jun 6. PMID: 24906372; PMCID: PMC4107328.
110. Lu A, Poddar M, Tang Y, Proto JD, Sohn J, Mu X, Oyster N, Wang B, Huard J. Rapid depletion of muscle progenitor cells in dystrophic mdx/utrophin-/- mice. Hum Mol Genet. 2014 Sep 15;23(18):4786-800. doi: 10.1093/hmg/ddu194. Epub 2014 Apr 29. PMID: 24781208; PMCID: PMC4140461.
111. Zhang M, McLennan IS. Use of antibodies to identify satellite cells with a light microscope. Muscle Nerve. 1994 Sep;17(9):987-94. doi: 10.1002/mus.880170905. PMID: 8065401.
112. Chang NC, Sincennes MC, Chevalier FP, Brun CE, Lacaria M, Segalés J, Muñoz-Cánoves P, Ming H, Rudnicki MA. The Dystrophin Glycoprotein Complex Regulates the Epigenetic Activation of Muscle Stem Cell Commitment. Cell Stem Cell. 2018 May 3;22(5):755-768.e6. doi: 10.1016/j.stem.2018.03.022. Epub 2018 Apr 19. PMID: 29681515; PMCID: PMC5935555.
113. Gosselin MRF, Mournetas V, Borczyk M, Verma S, Occhipinti A, Róg J, Bozycki L, Korostynski M, Robson SC, Angione C, Pinset C, Gorecki DC. Loss of full-length dystrophin expression results in major cell-autonomous abnormalities in proliferating myoblasts. Elife. 2022 Sep 27;11:e75521. doi: 10.7554/eLife.75521. PMID: 36164827; PMCID: PMC9514850.
114. Mournetas V, Massouridès E, Dupont JB, Kornobis E, Polvèche H, Jarrige M, Dorval ARL, Gosselin MRF, Manousopoulou A, Garbis SD, Górecki DC, Pinset C. Myogenesis modelled by human pluripotent stem cells: a multi-omic study of Duchenne myopathy early onset. J Cachexia Sarcopenia Muscle. 2021 Feb;12(1):209-232. doi: 10.1002/jcsm.12665. Epub 2021 Feb 14. PMID: 33586340; PMCID: PMC7890274.
115. Róg J, Oksiejuk A, Gosselin MRF, Brutkowski W, Dymkowska D, Nowak N, Robson S, Górecki DC, Zabłocki K. Dystrophic mdx mouse myoblasts exhibit elevated ATP/UTP-evoked metabotropic purinergic responses and alterations in calcium signalling. Biochim Biophys Acta Mol Basis Dis. 2019 Jun 1;1865(6):1138-1151. doi: 10.1016/j.bbadis.2019.01.002. Epub 2019 Jan 24. PMID: 30684640.
116. Róg J, Oksiejuk A, Górecki DC, Zabłocki K. Primary mouse myoblast metabotropic purinoceptor profiles and calcium signalling differ with their muscle origin and are altered in mdx dystrophinopathy. Sci Rep. 2023 Jun 8;13(1):9333. doi: 10.1038/s41598-023-36545-y. PMID: 37291185; PMCID: PMC10250391.
117. Shoji E, Sakurai H, Nishino T, Nakahata T, Heike T, Awaya T, Fujii N, Manabe Y, Matsuo M, Sehara-Fujisawa A. Early pathogenesis of Duchenne muscular dystrophy modelled in patient-derived human induced pluripotent stem cells. Sci Rep. 2015 Aug 20;5:12831. doi: 10.1038/srep12831. PMID: 26290039; PMCID: PMC4642533.
118. Yoshioka K, Ito A, Horie M, Ikeda K, Kataoka S, Sato K, Yoshigai T, Sakurai H, Hotta A, Kawabe Y, Kamihira M. Contractile Activity of Myotubes Derived from Human Induced Pluripotent Stem Cells: A Model of Duchenne Muscular Dystrophy. Cells. 2021 Sep 27;10(10):2556. doi:

10.3390/cells10102556. PMID: 34685536; PMCID: PMC8534131.

119. Onopiuk M, Brutkowski W, Wierzbicka K, Wojciechowska S, Szczepanowska J, Fronk J, Lochmüller H, Górecki DC, Zabłocki K. Mutation in dystrophin-encoding gene affects energy metabolism in mouse myoblasts. Biochem Biophys Res Commun. 2009 Aug 28;386(3):463-6. doi: 10.1016/j.bbrc.2009.06.053. Epub 2009 Jun 13. PMID: 19527684.
120. Pant M, Sopariwala DH, Bal NC, Lowe J, Delfín DA, Rafael-Fortney J, Periasamy M. Metabolic dysfunction and altered mitochondrial dynamics in the utrophin-dystrophin deficient mouse model of duchenne muscular dystrophy. PLoS One. 2015 Apr 10;10(4):e0123875. doi: 10.1371/journal.pone.0123875. PMID: 25859846; PMCID: PMC4393257.
121. Matre PR, Mu X, Wu J, Danila D, Hall MA, Kolonin MG, Darabi R, Huard J. CRISPR/Cas9-Based Dystrophin Restoration Reveals a Novel Role for Dystrophin in Bioenergetics and Stress Resistance of Muscle Progenitors. Stem Cells. 2019 Dec;37(12):1615-1628. doi: 10.1002/stem.3094. Epub 2019 Nov 18. PMID: 31574188; PMCID: PMC6916636.
122. Sugihara H, Teramoto N, Nakamura K, Shiga T, Shirakawa T, Matsuo M, Ogasawara M, Nishino I, Matsuwaki T, Nishihara M, Yamanouchi K. Cellular senescence-mediated exacerbation of Duchenne muscular dystrophy. Sci Rep. 2020 Oct 12;10(1):16385. doi: 10.1038/s41598-020-73315-6. PMID: 33046751; PMCID: PMC7550355.
123. Morgan J, Partridge T. Skeletal muscle in health and disease. Dis Model Mech. 2020 Feb 6;13(2):dmm042192. doi: 10.1242/dmm.042192. PMID: 32066552; PMCID: PMC7044447.
124. Partridge TA. Enhancing Interrogation of Skeletal Muscle Samples for Informative Quantitative Data. J Neuromuscul Dis. 2021;8(s2):S257-S269. doi: 10.3233/JND-210736. PMID: 34511511; PMCID: PMC8673506.
125. Gioftsidi S, Relaix F, Mourikis P. The Notch signaling network in muscle stem cells during development, homeostasis, and disease. Skelet Muscle. 2022 Apr 22;12(1):9. doi: 10.1186/s13395-022-00293-w. PMID: 35459219; PMCID: PMC9027478.
126. Ohlendieck K, Ervasti JM, Snook JB, Campbell KP. Dystrophin-glycoprotein complex is highly enriched in isolated skeletal muscle sarcolemma. J Cell Biol. 1991 Jan;112(1):135-48. doi: 10.1083/jcb.112.1.135. PMID: 1986002; PMCID: PMC2288808.
127. Ganassi M, Muntoni F, Zammit PS. Defining and identifying satellite cell-opathies within muscular dystrophies and myopathies. Exp Cell Res. 2022;411(1):112906. Epub 2021/11/07. doi: 10.1016/j.yexcr.2021.112906.
128. McLoon LK, Wirtschafter J. Activated satellite cells in extraocular muscles of normal adult monkeys and humans. Invest Ophthalmol Vis Sci. 2003 May;44(5):1927-32. doi: 10.1167/iovs.02-0673. PMID: 12714625; PMCID: PMC1796845.
129. Andrade FH, Porter JD, Kaminski HJ. Eye muscle sparing by the muscular dystrophies: lessons to be learned? Microsc Res Tech. 2000 Feb 1-15;48(3-4):192-203. doi: 10.1002/(SICI)1097-0029(20000201/15)48:3/4<192::AID-JEMT7>3.0.CO;2-J. PMID: 10679966.
130. McDonald AA, Kunz MD, McLoon LK. Dystrophic changes in extraocular muscles after gamma irradiation in mdx:utrophin(+/-) mice. PLoS One. 2014 Jan 21;9(1):e86424. doi: 10.1371/journal.pone.0086424. PMID: 24466085; PMCID: PMC3897728.
131. Stuelsatz P, Shearer A, Li Y, Muir LA, Ieronimakis N, Shen QW, Kirillova I, Yablonka-Reuveni Z. Extraocular muscle satellite cells are high performance myo-engines retaining efficient regenerative capacity in dystrophin deficiency. Dev Biol. 2015 Jan 1;397(1):31-44. doi: 10.1016/j.ydbio.2014.08.035. Epub 2014 Sep 16. PMID: 25236433; PMCID: PMC4309674.
132. Formicola L, Marazzi G, Sassoon DA. The extraocular muscle stem cell niche is resistant to ageing and disease. Front Aging Neurosci. 2014 Dec 1;6:328. doi: 10.3389/fnagi.2014.00328. PMID: 25520657; PMCID: PMC4249457.
133. Verma M, Fitzpatrick K, McLoon LK. Extraocular Muscle Repair and Regeneration. Curr Ophthalmol Rep. 2017 Sep;5(3):207-215. doi: 10.1007/s40135-017-0141-4. Epub 2017 Jun 16. PMID: 29109908; PMCID: PMC5669281.
134. Hernandez-Torres F, Rodríguez-Outeiriño L, Franco D, Aranega AE. Pitx2 in Embryonic and Adult Myogenesis. Front Cell Dev Biol. 2017 May 1;5:46. doi: 10.3389/fcell.2017.00046. PMID: 28507987; PMCID: PMC5410577.
135. Lewis C, Ohlendieck K. Proteomic profiling of naturally protected extraocular muscles from the dystrophin-deficient mdx mouse. Biochem Biophys Res Commun. 2010 Jun 11;396(4):1024-9. doi: 10.1016/j.bbrc.2010.05.052. Epub 2010 May 22. PMID: 20471957.
136. Matsumura CY, Menezes de Oliveira B, Durbeej M, Marques MJ. Isobaric Tagging-Based Quantification for Proteomic Analysis: A Comparative Study of Spared and Affected Muscles from mdx Mice at the Early Phase of Dystrophy. PLoS One. 2013 Jun 18;8(6):e65831. doi: 10.1371/journal.pone.0065831. PMID: 23823696; PMCID: PMC3688818.
137. Gargan S, Dowling P, Zweyer M, Reimann J, Henry M, Meleady P, Swandulla D, Ohlendieck K. Mass

Spectrometric Profiling of Extraocular Muscle and Proteomic Adaptations in the mdx-4cv Model of Duchenne Muscular Dystrophy. Life (Basel). 2021 Jun 22;11(7):595. doi: 10.3390/life11070595. PMID: 34206383; PMCID: PMC8304255.

138. Dowling P, Culligan K, Ohlendieck K. Distal mdx muscle groups exhibiting up-regulation of utrophin and rescue of dystrophin-associated glycoproteins exemplify a protected phenotype in muscular dystrophy. Naturwissenschaften. 2002 Feb;89(2):75-8. doi: 10.1007/s00114-001-0289-4. PMID: 12046625.
139. Dowling P, Lohan J, Ohlendieck K. Comparative analysis of Dp427-deficient mdx tissues shows that the milder dystrophic phenotype of extraocular and toe muscle fibres is associated with a persistent expression of beta-dystroglycan. Eur J Cell Biol. 2003 May;82(5):222-30. doi: 10.1078/0171-9335-00315. PMID: 12800977.
140. Ohlendieck K, Ervasti JM, Matsumura K, Kahl SD, Leveille CJ, Campbell KP. Dystrophin-related protein is localized to neuromuscular junctions of adult skeletal muscle. Neuron. 1991 Sep;7(3):499-508. doi: 10.1016/0896-6273(91)90301-f. PMID: 1654951.
141. Zeiger U, Mitchell CH, Khurana TS. Superior calcium homeostasis of extraocular muscles. Exp Eye Res. 2010 Nov;91(5):613-22. doi: 10.1016/j.exer.2010.07.019. Epub 2010 Aug 7. PMID: 20696159; PMCID: PMC4086352.
142. Zhang H, Liu Y, Li C, Zhang W. ITGβ6 Facilitates Skeletal Muscle Development by Maintaining the Properties and Cytoskeleton Stability of Satellite Cells. Life (Basel). 2022 Jun 21;12(7):926. doi: 10.3390/life12070926. PMID: 35888016; PMCID: PMC9318838.
143. Chen M, Zhang L, Guo Y, Liu X, Song Y, Li X, Ding X, Guo H. A novel lncRNA promotes myogenesis of bovine skeletal muscle satellite cells via PFN1-RhoA/Rac1. J Cell Mol Med. 2021 May 4;25(13):5988–6005. doi: 10.1111/jcmm.16427. Epub ahead of print. PMID: 33942976; PMCID: PMC8256363.
144. Baraibar M, Hyzewicz J, Rogowska-Wrzesinska A, Bulteau AL, Prip-Buus C, Butler-Browne G, Friguet B. Impaired metabolism of senescent muscle satellite cells is associated with oxidative modifications of glycolytic enzymes. Free Radic Biol Med. 2014 Oct;75 Suppl 1:S23. doi: 10.1016/j.freeradbiomed.2014.10.738. Epub 2014 Dec 10. PMID: 26461311.
145. Beauchamp JR, Heslop L, Yu DS, Tajbakhsh S, Kelly RG, Wernig A, Buckingham ME, Partridge TA, Zammit PS. Expression of CD34 and Myf5 defines the majority of quiescent adult skeletal muscle satellite cells. J Cell Biol. 2000 Dec 11;151(6):1221-34. doi: 10.1083/jcb.151.6.1221. PMID: 11121437; PMCID: PMC2190588.
146. Jankowski RJ, Deasy BM, Cao B, Gates C, Huard J. The role of CD34 expression and cellular fusion in the regeneration capacity of myogenic progenitor cells. J Cell Sci. 2002 Nov 15;115(Pt 22):4361-74. doi: 10.1242/jcs.00110. PMID: 12376567.
147. Fernández-Lázaro D, Garrosa E, Seco-Calvo J, Garrosa M. Potential Satellite Cell-Linked Biomarkers in Aging Skeletal Muscle Tissue: Proteomics and Proteogenomics to Monitor Sarcopenia. Proteomes. 2022 Aug 19;10(3):29. doi: 10.3390/proteomes10030029. PMID: 35997441; PMCID: PMC9396989.
148. Mansuri MS, Williams K, Nairn AC. Uncovering biology by single-cell proteomics. Commun Biol. 2023 Apr 8;6(1):381. doi: 10.1038/s42003-023-04635-2. PMID: 37031277; PMCID: PMC10082756.
149. Ahmad R, Budnik B. A review of the current state of single-cell proteomics and future perspective. Anal Bioanal Chem. 2023 Jun 7. doi: 10.1007/s00216-023-04759-8. Epub ahead of print. PMID: 37285026.
150. Slavov N. Scaling Up Single-Cell Proteomics. Mol Cell Proteomics. 2022 Jan;21(1):100179. doi: 10.1016/j.mcpro.2021.100179. Epub 2021 Nov 20. PMID: 34808355; PMCID: PMC8683604.
151. Petrosius V, Schoof EM. Recent advances in the field of single-cell proteomics. Transl Oncol. 2023 Jan;27:101556. doi: 10.1016/j.tranon.2022.101556. Epub 2022 Oct 19. PMID: 36270102; PMCID: PMC9587008.
152. Kim S, Kamarulzaman L, Taniguchi Y. Recent methodological advances towards single-cell proteomics. Proc Jpn Acad Ser B Phys Biol Sci. 2023 Sep 6. doi: 10.2183/pjab.99.021. Epub ahead of print. PMID: 37673661.
153. Rosenberger FA, Thielert M, Mann M. Making single-cell proteomics biologically relevant. Nat Methods. 2023 Mar;20(3):320-323. doi: 10.1038/s41592-023-01771-9. PMID: 36899157.
154. Wang Y, Lih TM, Chen L, Xu Y, Kuczler MD, Cao L, Pienta KJ, Amend SR, Zhang H. Optimized data-independent acquisition approach for proteomic analysis at single-cell level. Clin Proteomics. 2022 Jul 9;19(1):24. doi: 10.1186/s12014-022-09359-9. PMID: 35810282; PMCID: PMC9270744.
155. Mun DG, Bhat FA, Ding H, Madden BJ, Natesampillai S, Badley AD, Johnson KL, Kelly RT, Pandey A. Optimizing single cell proteomics using trapped ion mobility spectrometry for label-free experiments. Analyst. 2023 Jul 26;148(15):3466-3475. doi: 10.1039/d3an00080j. PMID: 37395315; PMCID: PMC10370902.
156. Cong Y, Motamedchaboki K, Misal SA, Liang Y, Guise AJ, Truong T, Huguet R, Plowey ED, Zhu Y, Lopez-Ferrer D, Kelly RT. Ultrasensitive single-cell proteomics workflow identifies >1000 protein groups per mammalian cell. Chem Sci. 2020 Nov

17;12(3):1001-1006. doi: 10.1039/d0sc03636f. PMID: 34163866; PMCID: PMC8178986.
157. Murgia M, Nogara L, Baraldo M, Reggiani C, Mann M, Schiaffino S. Protein profile of fiber types in human skeletal muscle: a single-fiber proteomics study. Skelet Muscle. 2021 Nov 2;11(1):24. doi: 10.1186/s13395-021-00279-0. PMID: 34727990; PMCID: PMC8561870.
158. Murgia M, Ciciliot S, Nagaraj N, Reggiani C, Schiaffino S, Franchi MV, Pišot R, Šimunič B, Toniolo L, Blaauw B, Sandri M, Biolo G, Flück M, Narici MV, Mann M. Signatures of muscle disuse in spaceflight and bed rest revealed by single muscle fiber proteomics. PNAS Nexus. 2022 Jun 11;1(3):pgac086. doi: 10.1093/pnasnexus/pgac086. PMID: 36741463; PMCID: PMC9896895.
159. Schiaffino S, Reggiani C, Murgia M. Fiber type diversity in skeletal muscle explored by mass spectrometry-based single fiber proteomics. Histol Histopathol. 2020 Mar;35(3):239-246. doi: 10.14670/HH-18-170. Epub 2019 Oct 15. PMID: 31612964.
160. Momenzadeh A, Jiang Y, Kreimer S, Teigen LE, Zepeda CS, Haghani A, Mastali M, Song Y, Hutton A, Parker SJ, Van Eyk JE, Sundberg CW, Meyer JG. A Complete Workflow for High Throughput Human Single Skeletal Muscle Fiber Proteomics. J Am Soc Mass Spectrom. 2023 Sep 6;34(9):1858-1867. doi: 10.1021/jasms.3c00072. Epub 2023 Jul 18. PMID: 37463334.
161. Borok M, Didier N, Gattazzo F, Ozturk T, Corneau A, Rouard H, Relaix F. Progressive and Coordinated Mobilization of the Skeletal Muscle Niche throughout Tissue Repair Revealed by Single-Cell Proteomic Analysis. Cells. 2021 Mar 28;10(4):744. doi: 10.3390/cells10040744. PMID: 33800595; PMCID: PMC8066646.
162. Fabre P, Molina T, Orfi Z, Dumont NA. Assessment of Muscle Function Following hiPSC-Derived Myoblast Transplantation in Dystrophic Mice. Curr Protoc. 2022 Jan;2(1):e356. doi: 10.1002/cpz1.356. Erratum in: Curr Protoc. 2022 Aug;2(8):e554. PMID: 35085428.
163. Fortunato F, Farnè M, Ferlini A. The DMD gene and therapeutic approaches to restore dystrophin. Neuromuscul Disord. 2021 Oct;31(10):1013-1020. doi: 10.1016/j.nmd.2021.08.004. PMID: 34736624.
164. Fortunato F, Rossi R, Falzarano MS, Ferlini A. Innovative Therapeutic Approaches for Duchenne Muscular Dystrophy. J Clin Med. 2021 Feb 17;10(4):820. doi: 10.3390/jcm10040820. PMID: 33671409; PMCID: PMC7922390.
165. Górecki DC. Dystrophin immunogenicity and requirement in myogenic cells: Paradigm shift in gene therapy for DMD. Clin Transl Med. 2022 Nov;12(11):e1122. doi: 10.1002/ctm2.1122. PMID: 36424805; PMCID: PMC9691905.
166. Saleh KK, Switzler C, Hicks MR, Gane L, Gibbs DE, Pyle AD. Duchenne muscular dystrophy disease severity impacts skeletal muscle progenitor cells systemic delivery. Front Physiol. 2023 May 9;14:1190524. doi: 10.3389/fphys.2023.1190524. PMID: 37228827; PMCID: PMC10203213.
167. Partridge TA, Morgan JE. Multiple insights from myogenic cell transplants. Hum Gene Ther. 2014 May;25(5):404-5. doi: 10.1089/hum.2014.035. PMID: 24848316.
168. Dumont NA, Rudnicki MA. Targeting muscle stem cell intrinsic defects to treat Duchenne muscular dystrophy. NPJ Regen Med. 2016;1:16006–. doi: 10.1038/npjregenmed.2016.6. Epub 2016 Jun 9. PMID: 29188075; PMCID: PMC5703417.
169. Filippelli RL, Chang NC. Empowering Muscle Stem Cells for the Treatment of Duchenne Muscular Dystrophy. Cells Tissues Organs. 2022;211(6):641-654. doi: 10.1159/000514305. Epub 2021 Apr 28. PMID: 33910206.
170. Boyer O, Butler-Browne G, Chinoy H, Cossu G, Galli F, Lilleker JB, Magli A, Mouly V, Perlingeiro RCR, Previtali SC, Sampaolesi M, Smeets H, Schoewel-Wolf V, Spuler S, Torrente Y, Van Tienen F; Study Group. Myogenic Cell Transplantation in Genetic and Acquired Diseases of Skeletal Muscle. Front Genet. 2021 Aug 2;12:702547. doi: 10.3389/fgene.2021.702547. PMID: 34408774; PMCID: PMC8365145.
171. Galli F, Mouly V, Butler-Browne G, Cossu G. Challenges in cell transplantation for muscular dystrophy. Exp Cell Res. 2021 Dec 1;409(1):112908. doi: 10.1016/j.yexcr.2021.112908. Epub 2021 Nov 1. PMID: 34736920.
172. Sun C, Serra C, Lee G, Wagner KR. Stem cell-based therapies for Duchenne muscular dystrophy. Exp Neurol. 2020 Jan;323:113086. doi: 10.1016/j.expneurol.2019.113086. Epub 2019 Oct 19. PMID: 31639376; PMCID: PMC6899334.
173. Ausems CRM, van Engelen BGM, van Bokhoven H, Wansink DG. Systemic cell therapy for muscular dystrophies : The ultimate transplantable muscle progenitor cell and current challenges for clinical efficacy. Stem Cell Rev Rep. 2021 Jun;17(3):878-899. doi: 10.1007/s12015-020-10100-y. Epub 2020 Dec 21. PMID: 33349909; PMCID: PMC8166694.
174. Vallejo D, Hernández-Torres F, Lozano-Velasco E, Rodriguez-Outeiriño L, Carvajal A, Creus C, Franco D, Aránega AE. PITX2 Enhances the Regenerative Potential of Dystrophic Skeletal Muscle Stem Cells. Stem Cell Reports. 2018 Apr 10;10(4):1398-1411. doi: 10.1016/j.stemcr.2018.03.009. PMID: 29641992; PMCID: PMC5998647.
175. McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F, Clemens PR, Hoffman EP, Cnaan A, Gordish-Dressman H; CINRG

Investigators. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 2018 Feb 3;391(10119):451-461. doi: 10.1016/S0140-6736(17)32160-8. Epub 2017 Nov 22. PMID: 29174484.

176. Merlini L, Cecconi I, Parmeggiani A, Cordelli DM, Dormi A. Quadriceps muscle strength in Duchenne muscular dystrophy and effect of corticosteroid treatment. Acta Myol. 2020 Dec 1;39(4):200-206. doi: 10.36185/2532-1900-023. PMID: 33458575; PMCID: PMC7783426.
177. Hoffman EP. Pharmacotherapy of Duchenne Muscular Dystrophy. Handb Exp Pharmacol. 2020;261:25-37. doi: 10.1007/164_2019_256. PMID: 31375923.
178. Grages SM, Bell M, Berlau DJ. New and emerging pharmacotherapy for duchenne muscular dystrophy: a focus on synthetic therapeutics. Expert Opin Pharmacother. 2020 May;21(7):841-851. doi: 10.1080/14656566.2020.1732350. Epub 2020 Mar 5. PMID: 32133879.
179. Kawamura K, Fukumura S, Nikaido K, Tachi N, Kozuka N, Seino T, Hatakeyama K, Mori M, Ito YM, Takami A, Hinotsu S, Kuno A, Kawasaki Y, Horio Y, Tsutsumi H. Resveratrol improves motor function in patients with muscular dystrophies: an open-label, single-arm, phase IIa study. Sci Rep. 2020 Nov 25;10(1):20585. doi: 10.1038/s41598-020-77197-6. PMID: 33239684; PMCID: PMC7688653.
180. Amor F, Vu Hong A, Corre G, Sanson M, Suel L, Blaie S, Servais L, Voit T, Richard I, Israeli D. Cholesterol metabolism is a potential therapeutic target in Duchenne muscular dystrophy. J Cachexia Sarcopenia Muscle. 2021 Jun;12(3):677-693. doi: 10.1002/jcsm.12708. Epub 2021 May 26. PMID: 34037326; PMCID: PMC8200436.
181. Ziemba M, Barkhouse M, Uaesoontrachoon K, Giri M, Hathout Y, Dang UJ, Gordish-Dressman H, Nagaraju K, Hoffman EP. Biomarker-focused multi-drug combination therapy and repurposing trial in mdx mice. PLoS One. 2021 Feb 22;16(2):e0246507. doi: 10.1371/journal.pone.0246507. PMID: 33617542; PMCID: PMC7899329.
182. Doran P, Wilton SD, Fletcher S, Ohlendieck K. Proteomic profiling of antisense-induced exon skipping reveals reversal of pathobiochemical abnormalities in dystrophic mdx diaphragm. Proteomics. 2009 Feb;9(3):671-85. doi: 10.1002/pmic.200800441. PMID: 19132684; PMCID: PMC2770591.
183. Li D, Mastaglia FL, Fletcher S, Wilton SD. Precision Medicine through Antisense Oligonucleotide-Mediated Exon Skipping. Trends Pharmacol Sci. 2018 Nov;39(11):982-994. doi: 10.1016/j.tips.2018.09.001. Epub 2018 Sep 30. PMID: 30282590.
184. Clemens PR, Rao VK, Connolly AM, Harper AD, Mah JK, Smith EC, McDonald CM, Zaidman CM, Morgenroth LP, Osaki H, Satou Y, Yamashita T, Hoffman EP; CINRG DNHS Investigators. Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A Phase 2 Randomized Clinical Trial. JAMA Neurol. 2020 Aug 1;77(8):982-991. doi: 10.1001/jamaneurol.2020.1264. Erratum in: JAMA Neurol. 2020 Aug 1;77(8):1040. PMID: 32453377; PMCID: PMC7251505.
185. Novak JS, Spathis R, Dang UJ, Fiorillo AA, Hindupur R, Tully CB, Mázala DAG, Canessa E, Brown KJ, Partridge TA, Hathout Y, Nagaraju K. Interrogation of Dystrophin and Dystroglycan Complex Protein Turnover After Exon Skipping Therapy. J Neuromuscul Dis. 2021;8(s2):S383-S402. doi: 10.3233/JND-210696. PMID: 34569969; PMCID: PMC8673539.
186. Vila MC, Novak JS, Benny Klimek M, Li N, Morales M, Fritz AG, Edwards K, Boehler JF, Hogarth MW, Kinder TB, Zhang A, Mazala D, Fiorillo AA, Douglas B, Chen YW, van den Anker J, Lu QL, Hathout Y, Hoffman EP, Partridge TA, Nagaraju K. Morpholino-induced exon skipping stimulates cell-mediated and humoral responses to dystrophin in mdx mice. J Pathol. 2019 Jul;248(3):339-351. doi: 10.1002/path.5263. Epub 2019 Apr 16. PMID: 30883742; PMCID: PMC6579705.
187. Novak JS, Hogarth MW, Boehler JF, Nearing M, Vila MC, Heredia R, Fiorillo AA, Zhang A, Hathout Y, Hoffman EP, Jaiswal JK, Nagaraju K, Cirak S, Partridge TA. Myoblasts and macrophages are required for therapeutic morpholino antisense oligonucleotide delivery to dystrophic muscle. Nat Commun. 2017 Oct 16;8(1):941. doi: 10.1038/s41467-017-00924-7. Erratum in: Nat Commun. 2018 Jan 15;9(1):208. Erratum in: Nat Commun. 2018 Mar 23;9(1):1256. PMID: 29038471; PMCID: PMC5643396.
188. Min YL, Bassel-Duby R, Olson EN. CRISPR Correction of Duchenne Muscular Dystrophy. Annu Rev Med. 2019 Jan 27;70:239-255. doi: 10.1146/annurev-med-081117-010451. Epub 2018 Oct 31. PMID: 30379597; PMCID: PMC6415693.
189. Kupatt C, Windisch A, Moretti A, Wolf E, Wurst W, Walter MC. Genome editing for Duchenne muscular dystrophy: a glimpse of the future? Gene Ther. 2021 Sep;28(9):542-548. doi: 10.1038/s41434-021-00222-4. Epub 2021 Feb 2. PMID: 33531685; PMCID: PMC8455335.
190. Domenig SA, Bundschuh N, Lenardič A, Ghosh A, Kim I, Qabrati X, D'Hulst G, Bar-Nur O. CRISPR/Cas9 editing of directly reprogrammed myogenic progenitors restores dystrophin

expression in a mouse model of muscular dystrophy. Stem Cell Reports. 2022 Feb 8;17(2):321-336. doi: 10.1016/j.stemcr.2021.12.003. Epub 2022 Jan 6. PMID: 34995499; PMCID: PMC8828535.

191. Politano L. Read-through approach for stop mutations in Duchenne muscular dystrophy. An update. Acta Myol. 2021 Mar 31;40(1):43-50. doi: 10.36185/2532-1900-041. PMID: 33870095; PMCID: PMC8033424.
192. Sun C, Shen L, Zhang Z, Xie X. Therapeutic Strategies for Duchenne Muscular Dystrophy: An Update. Genes (Basel). 2020 Jul 23;11(8):837. doi: 10.3390/genes11080837. PMID: 32717791; PMCID: PMC7463903.
193. Seto JT, Ramos JN, Muir L, Chamberlain JS, Odom GL (2012) Gene replacement therapies for duchenne muscular dystro- phy using adeno-associated viral vectors. Curr Gene Ther 12:139-151.
194. Nance ME, Duan D. Perspective on Adeno-Associated Virus Capsid Modification for Duchenne Muscular Dystrophy Gene Therapy. Hum Gene Ther. 2015 Dec;26(12):786-800. doi: 10.1089/hum.2015.107. Epub 2015 Oct 15. PMID: 26414293; PMCID: PMC4692109.
195. Zhang Y, Yue Y, Li L, Hakim CH, Zhang K, Thomas GD, Duan D. Dual AAV therapy ameliorates exercise-induced muscle injury and functional ischemia in murine models of Duchenne muscular dystrophy. Hum Mol Genet. 2013 Sep 15;22(18):3720-9. doi: 10.1093/hmg/ddt224. Epub 2013 May 15. PMID: 23681067; PMCID: PMC3749861.
196. Loro E, Sengupta K, Bogdanovich S, Whig K, Schultz DC, Huryn DM, Khurana TS. High-throughput identification of post-transcriptional utrophin up-regulators for Duchenne muscle dystrophy (DMD) therapy. Sci Rep. 2020 Feb 7;10(1):2132. doi: 10.1038/s41598-020-58737-6. Erratum in: Sci Rep. 2020 Feb 28;10(1):4039. PMID: 32034254; PMCID: PMC7005813.
197. Soblechero-Martín P, López-Martínez A, de la Puente-Ovejero L, Vallejo-Illarramendi A, Arechavala-Gomeza V. Utrophin modulator drugs as potential therapies for Duchenne and Becker muscular dystrophies. Neuropathol Appl Neurobiol. 2021 Oct;47(6):711-723. doi: 10.1111/nan.12735. Epub 2021 Jun 4. PMID: 33999469; PMCID: PMC8518368.
198. Vuorinen A, Wilkinson IVL, Chatzopoulou M, Edwards B, Squire SE, Fairclough RJ, Bazan NA, Milner JA, Conole D, Donald JR, Shah N, Willis NJ, Martínez RF, Wilson FX, Wynne GM, Davies SG, Davies KE, Russell AJ. Discovery and mechanism of action studies of 4,6-diphenylpyrimidine-2-carbohydrazides as utrophin modulators for the treatment of Duchenne muscular dystrophy. Eur J Med Chem. 2021 Aug 5;220:113431. doi: 10.1016/j.ejmech.2021.113431. Epub 2021 Apr 20. PMID: 33915371.
199. Gehrig SM, van der Poel C, Sayer TA, Schertzer JD, Henstridge DC, Church JE, Lamon S, Russell AP, Davies KE, Febbraio MA, Lynch GS. Hsp72 preserves muscle function and slows progression of severe muscular dystrophy. Nature. 2012 Apr 4;484(7394):394-8. doi: 10.1038/nature10980. PMID: 22495301.
200. Thakur SS, Swiderski K, Ryall JG, Lynch GS. Therapeutic potential of heat shock protein induction for muscular dystrophy and other muscle wasting conditions. Philos Trans R Soc Lond B Biol Sci. 2018 Jan 19;373(1738):20160528. doi: 10.1098/rstb.2016.0528. PMID: 29203713; PMCID: PMC5717528.
201. Hardee JP, Martins KJB, Miotto PM, Ryall JG, Gehrig SM, Reljic B, Naim T, Chung JD, Trieu J, Swiderski K, Philp AM, Philp A, Watt MJ, Stroud DA, Koopman R, Steinberg GR, Lynch GS. Metabolic remodeling of dystrophic skeletal muscle reveals biological roles for dystrophin and utrophin in adaptation and plasticity. Mol Metab. 2021 Mar;45:101157. doi: 10.1016/j.molmet.2020.101157. Epub 2020 Dec 24. PMID: 33359740; PMCID: PMC7811171.
202. Serrano AL, Muñoz-Cánoves P. Fibrosis development in early-onset muscular dystrophies: Mechanisms and translational implications. Semin Cell Dev Biol. 2017 Apr;64:181-190. doi: 10.1016/j.semcdb.2016.09.013. Epub 2016 Sep 23. PMID: 27670721.
203. March JT, Golshirazi G, Cernisova V, Carr H, Leong Y, Lu-Nguyen N, Popplewell LJ. Targeting TGFβ Signaling to Address Fibrosis Using Antisense Oligonucleotides. Biomedicines. 2018 Jun 25;6(3):74. doi: 10.3390/biomedicines6030074. PMID: 29941814; PMCID: PMC6164894.

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